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Cisplatin-induced emesis: systematic review and meta-analysis of the ferret model and the effects of 5-HT₃ receptor antagonists.

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Running title:

Meta-analysis of cisplatin emesis in the ferret

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SUMMARY

Purpose:

The ferret cisplatin emesis model has been used for ~30 years and enabled identification of clinically used anti-emetics. We provide an objective assessment of this model including efficacy of 5-HT₃ receptor antagonists to assess its translational validity.

Methods:

A systematic review identified available evidence and was used to perform meta-analyses.

Results:

Of 182 potentially relevant publications, 115 reported cisplatin-induced emesis in ferrets and 68 were included in the analysis. The majority (n=53) used a 10 mg.kg⁻¹ dose to induce acute emesis, which peaked after 2h. More recent studies (n=11) also used 5 mg.kg⁻¹, which induced a biphasic response peaking at 12h and 48h. Overall, 5-HT₃ receptor antagonists reduced cisplatin (5 mg.kg⁻¹) emesis by 68% (45-91%) during the acute phase (day 1) and by 67% (48-86%) and 53% (38-68%, all p<0.001), during the delayed phase (days 2 and 3). In an analysis focused on the acute phase, the efficacy of ondansetron was dependent on the dosage and observation period but not on the dose of cisplatin.

Conclusion:

Our analysis enabled novel findings to be extracted from the literature including factors, which may impact on the applicability of preclinical results to humans. It reveals that the efficacy of ondansetron is similar against low and high doses of cisplatin. Additionally, we showed that 5-HT₃ receptor antagonists have a similar efficacy during acute and delayed emesis, which provides a novel insight into the pharmacology of delayed emesis in the ferret.

Keywords.

Cisplatin; emesis; ferret; meta-analysis; systematic review; ondansetron; 5-HT₃ receptor antagonist; granisetron; tropisetron.

Abbreviations:

5-HT₃: 5-hydroxytryptamine₃; NK₁: neurokinin₁; i.v.: intravenous; i.p.: intraperitoneal; p.o.: *per os*, oral; s.c.: sub-cutaneous; R+V: retches and vomits; SD: standard deviation; CI: confidence interval

1 INTRODUCTION

It is generally accepted that nausea and vomiting (emesis) are components of a protective mechanism by which the human body defends itself against ingested toxins. However, the emetic reflex can be triggered inappropriately and nausea and vomiting are also relatively common side effects of drugs in current use (e.g. morphine, anti-cancer chemotherapy) as well as dose-limiting toxicities which may limit the development of novel chemical entities intended for the treatment of a range of diseases (e.g. phosphodiesterase-IV inhibitors for the treatment of asthma [135]).

The multi-system nature of the emetic reflex coordinated in the brainstem and the behavioural and sensory expression of nausea have meant that, to date, preclinical studies of the mechanisms involved and identification of novel anti-emetic agents have involved studies in whole animals (conscious, anaesthetised or decerebrate) [61]. Nausea and vomiting are particularly associated with the treatment of cancer by cytotoxic drugs (e.g. cisplatin), symptoms which patients find particularly distressing and impact upon compliance with treatment. In the absence of anti-emetic prophylaxis, cisplatin induces nausea and vomiting in virtually all patients [109]; the emetic response lasts up to 5 days on each cycle and is characterised by an intense acute phase lasting ~24 hours and a less intense but more protracted delayed phase peaking during the period 48-72 hours following the administration of cisplatin [72].

In the early 1980's the ferret (*Mustela putorius furo* L.) was reported to develop an acute emetic response to high dose cisplatin (8-10 mg.kg⁻¹) and was proposed as an alternative model to the dog, cat and monkey (commonly used at the time) to study cytotoxic drug-induced emesis and identify potential anti-emetic agents [40].

Subsequently the acute cisplatin model was modified and the dose of cisplatin lowered to 5 mg.kg⁻¹ to investigate delayed emesis [114]. The ferret model of cisplatin-induced emesis was rapidly adopted for the investigation of new anti-emetic agents and was pivotal in establishing the anti-emetic efficacy of 5-

hydroxytryptamine₃ (5-HT₃) [94] and tachykinin NK₁ receptor antagonists [148], which are both currently in widespread use for the treatment of chemotherapy-induced nausea and vomiting [109].

The use and benefit of animal models in research is regularly questioned and anecdotal evidence or unsupported claims, as opposed to quantitative support, are too often used as justifications [88, 105]. There has recently been a growing interest in systematic reviews and meta-analyses to assess the validity of animal models (i.e. how preclinical research has informed clinical research) and their utility in drug discovery (i.e. evaluate data and inform the decision to carry out a clinical trial). The Nuffield Council for Bioethics [101] recommends that such reviews are undertaken to “evaluate more fully the predictability and transferability of animal model”. Such analyses also have implications for the application of the principles of the 3Rs (Replacement, Refinement, Reduction) to animal experimentation [61, 68] and should inform preclinical guidelines produced by regulators [e.g. 37]. Recently, systematic reviews and meta-analysis of animal models of stroke have been carried out. A retrospective study concluded that even though individual studies had reported beneficial effects of the calcium channel blocker nimodipine, overall the preclinical data available were not conclusive [62], which is consistent with the fact that this type of drug was without effect in humans [63] and highlights the necessity of quantifying animal data adequately before starting clinical trials. Later studies assessed the preclinical evidence of the effect of potential treatments in experimental stroke and characterised their neuroprotective properties in order to identify research priorities [78-80].

The cisplatin-induced emesis ferret models provide a unique opportunity to assess the value of systematic reviews in specific areas, because the wealth of data available in this relatively circumscribed area allows assessment of two characteristics of a model: the response to cisplatin itself, and the anti-emetic potential of agents that are currently used in humans. The aim of this systematic

review is two-fold: firstly, this study intends to provide an objective measure of the characteristics of cisplatin-induced emesis in the ferret, in terms of the latency, magnitude (number of retches and vomits) and profile of the emetic response. Secondly, the effect of 5-HT₃ receptor antagonists in the ferret model will be quantified; the present study will assess the efficacy of ondansetron against the acute phase of emesis; additionally, we will compare the overall effect of 5-HT₃ receptors antagonists against the acute and delayed phases of emesis.

This paper is the first systematic review and meta-analysis covering a model of emesis and anti-emetics. It provides evidence, which supports the predictability of the model and identifies new features of the model not apparent from individual studies. Additionally it shows the limitations of the model and identifies opportunities for enhanced animal welfare according to the principles of the “3Rs” formulated by Russell and Burch over 50 years ago [126].

2 METHODS

Search strategy

Studies were identified from Pubmed (1974 to March 2007) and Embase (1980 to March 2007) using the combination of words: CISPLATIN and FERRET; hand searching of abstracts of scientific meetings and personal files. All references of newly identified publications were also screened until no further eligible references were found. Language was not restricted. Values for data expressed graphically were either requested from authors or measured from the graphs. Corresponding authors were also contacted to obtain data that was not reported clearly enough in their publications.

Inclusion criteria:

- Report of cisplatin-induced emesis in the ferret
- Emetic response documented, and quantified by at least one of the following:

latency to onset of emesis (retching or vomiting), number of animals developing emesis, number of retches (R), vomits (V), retches and vomits (R+V) defined according to our definition and reported as mean only or mean \pm SEM or SD, and number of ferrets per group.

Exclusion criteria:

- Number of animals not stated
- Emetic response investigated under anaesthesia
- Emetic response not reported as the number of animals developing emesis,

or mean latency, or mean number of retches and vomits compatible with the standard definition of emesis.

Emesis was defined as retching (i.e. rhythmic abdominal contractions against a closed glottis) and vomiting (i.e. rhythmic abdominal contractions associated with the oral expulsion of solid or liquid materials from the gastrointestinal tract) [14, 22, 89].

Reports stating this definition in their methods section were included in this study; if

the definition was absent or unclear, evaluation of the results reported and their inclusion in this quantitative review were left to the judgement of the investigator and discussed with co-workers; reports were included:

- If the same team had published other reports clearly stating this definition or a member of the team—most senior or corresponding author—was contacted to confirm the definition used to characterise emesis.
- If the report referred to publications clearly stating this definition.
- If the definition stated allowed the identification of the number of retches and/or vomits according to our definition.

The latency (time to onset of emesis) was a potential confounding factor as many publications reported the latency as a mean for all the animals in the groups, including those free of emesis, in which case the latency was taken as the total duration of the observation time. All latencies were recalculated as the mean latency to the 1st retch or vomit in animals that developed emesis only. The latency was either measured as the time to the first retch, the time to the first vomit or the time to the first emetic episode. All the latencies reported were included combined together, as it was considered that only a minimal period of time separates the first retch from the first vomit [144], a more rigid approach including only the studies with either one or the other measurement and excluding those reporting the latency to the first emesis or emetic episode would have induced a greater error.

Data extraction and analysis

Meta-analysis: the ferret model of cisplatin-induced emesis

The number of retches (R), vomits (V), retches + vomits (R+V) and/or latency data from control groups (i.e. animals that received no other drug than cisplatin or cisplatin and an inactive—i.e. non-emetogenic—vehicle) were extracted as mean, standard deviations (SD) and number of animals per group. Weighted mean and weighted mean of the SD were calculated and a one-way ANOVA was carried out to compare

the onset of emesis following different doses of cisplatin. Unless stated, all results are reported as mean \pm SD. In order to identify variables modulating the emetic response, subgroup analyses were carried out according to criteria such as the vehicle used, duration of the observation period, the mode of administration of cisplatin (i.v. or i.p.), the use of anaesthesia and the recovery time prior to the emetic challenge, the strain (fitch or albino), sex and origin of the ferrets. This analysis was only carried out on the most common doses of cisplatin used to induce acute (10 mg.kg⁻¹) and acute and delayed emesis in the ferret (5 mg.kg⁻¹); the two doses were treated separately. Weighted means and the weighted mean of the SDs were calculated and profiles of emesis were constructed with Graphpad Prism® version 5.0, Graphpad Software Inc., San Diego, USA. Differences were assessed by a one-way analysis of variance (ANOVA) or independent sample t-tests as appropriate. Descriptive statistics and comparisons were carried out using SPSS® 14.00, SPSS Inc., Chicago, USA and CLINSTAT (M. Bland). Differences were considered statistically significant when $p < 0.05$.

Meta-analysis: the effect of anti-emetics

For the meta-analysis of the effects of anti-emetics, comparisons were only included if the effect of a prophylactic anti-emetic treatment was reported, the 3 outcomes measured were: the number of R+V, proportion of animals experiencing emesis and latency to the onset of emesis. To calculate the effect size and its 95% confidence interval for the continuous outcomes (i.e. R+V and latency), the mean outcome for the treatment group, and the SDs in treatment and control groups were expressed as a proportion of the outcome in the control group [80]. Actual data were used for dichotomous outcomes (i.e. the number of animals with emesis). When a control group was used to assess more than one treatment group, the number of animals in the control group was divided by the number of treatment groups and if needed, adjusted to the next integer. This methodology is consistent with what has been done in another meta-analysis of animal data in a model of stroke [80]. The effect of

ondansetron was examined for each of the 3 outcomes; subgroup analyses were carried out depending on the dose of cisplatin and duration of the observation period, dose, timing and mode of administration of ondansetron, mode of administration of cisplatin, origin of the ferrets, and quality score of the study. Additional analyses examined the effects of 5-HT₃ receptor antagonists on the latency to the onset of cisplatin (10 mg.kg⁻¹)-induced emesis and on the acute and delayed R+V induced by 5 mg.kg⁻¹ cisplatin (criteria for variation: individual compound). In the later analysis, comparisons on a given day were only included if the anti-emetic treatment started before or at the start of the 24h period and was continued throughout the day. Methodological quality of individual studies was assessed according to criteria chosen to evaluate the reliability of the data extracted. These criteria were: no duplicate publication identified—confirmed or suspected—, retch and vomit clearly defined or definition confirmed by authors, latency to the 1st retch or vomit given, SEM/SD given for the mean latency, number of retches and vomits or R+V given, SEM/SD given for the mean R+V, number of ferrets completely protected given (1 point per criterion fulfilled), origin, sex, strain and body weight of the ferrets given (1/2 point per criterion fulfilled). Each study was given a quality score out of a possible total of 9 points. The DerSimonian and Laird method was used to combine dichotomous (risk difference [RD]) and continuous data (weighted mean difference [WMD]). The random-effects model was chosen over the fixed effect assumption because it incorporates inter-study differences into the analysis of the overall treatment efficacy [28]. The data were analyzed with Review Manager (RevMan. Version 5.0 for Macintosh. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). All effect estimates are reported as mean and 95% confidence intervals. Z-tests were used to assess the overall effect of treatments and Chi-squared (χ^2) tests were used to assess the heterogeneity along with I², which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than chance (a value greater than 50% may be considered

substantial heterogeneity). The differences between the treatment effects of sub-categories of a particular outcome were assessed by a Z-test [1, 87], potential publication biases were assessed by Funnel plots [143].

Anti-emetic drugs examined

Ondansetron: 9-methyl-3-[(2-methylimidazol-1-yl)methyl]-2,3-dihydro-1H-carbazol-4-one. Granisetron: 1-methyl-N-(9-methyl-9-azabicyclo[3.3.1]nonan-7-yl)indazole-3-carboxamide. Ondansetron: N-(3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)-1H-indazole-3-carboxamide. Zacopride: 4-amino-N-(1-azabicyclo[2.2.2]octan-8-yl)-5-chloro-2-methoxybenzamide. FK1052: (7S)-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]-8,9-dihydro-7H-pyrido[1,2-a]indol-6-one hydrochloride. Dolasetron: (3R)-10-oxo-8-azatricyclo[5.3.1.0^{3,8}]undec-5-yl 1H-indole-3-carboxylate. L-683,877: 2¹-(1-Methyl-1H-indol-3-yl)-)spiro(1-azabicyclo[2.2.2]octane-3,5¹ (4¹H)-oxazole. Ramosetron: (1-methylindol-3-yl)-[(5R)-4,5,6,7-tetrahydro-3H-benzimidazol-5-yl]methanone. Azasetron: N-(1-azabicyclo[2.2.2]octan-8-yl)-6-chloro-4-methyl-3-oxo-1,4-benzoxazine-8-carboxamide. Renzapride: 4-amino-N-[(5S,6S)-1-azabicyclo[3.3.1]nonan-6-yl]-5-chloro-2-methoxybenzamide. Bemisetron: [(1S,5R)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl] 3,5-dichlorobenzoate.

3 RESULTS

Publications

As of March 2007, 182 publications were retrieved, 115 publications describing cisplatin-induced emesis in the ferret were identified, 32 publications were excluded and 83 publications contained usable data (Figure 1, Tables 1 and 2). A further 15 publications were excluded on the grounds that data was already reported elsewhere. The remaining 68 publications were either fully or partly included as some papers presented original data and duplicate data together, in this case only the original data was extracted and the duplicate data was ignored.

Out of the 68 publications from which at least one outcome was extracted, 44, 10 and 9 publications reported the effect of at least one 5-HT₃, NK₁ receptor antagonist and glucocorticoid, respectively. In terms of outcome, 63 studies reported the latency, which was either measured as the latency to the first retch (13% of the publications reporting the latency), the latency to the first vomit (16%) or the latency to the first emetic episode (75%). Fifty-one studies reported the number of retches and vomits (R+V) in a given observation time, 37 and 36 studies respectively reported the number of retches and vomits separately. The number of animals with emesis during the duration of the observation time was reported in 45 publications.

Meta-analysis: the ferret model of cisplatin induced emesis

Dose of cisplatin

The latency to the onset of emesis was dose-dependant; the time of onset was significantly delayed following a dose of cisplatin of 5 mg.kg⁻¹, compared with higher doses (6-20 mg.kg⁻¹, one-way ANOVA followed by Bonferroni post-tests, see Figure 2). Additionally differences between the doses of 6 to 20 mg.kg⁻¹ were detected (p<0.001, one way ANOVA) and the latency shortened when the dose increased.

The 10 mg.kg⁻¹ cisplatin model

The duration of the observation period varied from 2 to 40h (at which time the animals were killed). The most common observation period was 4h, during which 107 ± 48 R+V (n=199, 22 studies) were observed. In studies using 2h, 3h, 6h, 24h and 40h observation periods, 79 ± 35 R+V (n=40, 6 studies), 101 ± 48 R+V (n=29, 3 studies), 170 ± 56 R+V (n=73, 8 studies), 204 ± 52 R+V (n=16, 3 studies) and 188 R+V (n=4, 1 study) were observed, respectively. The number of R+V significantly increased as the observation period increased up to 24h (one-way ANOVA, $p < 0.001$). The intensity of emesis reached a maximum after 2h and decreased to a very low level (less than 5 R+V per hour) from 3h onward post cisplatin (Figure 3A). The latency to the onset of emesis was shorter when cisplatin was administered intravenously (1.16 ± 0.35 h, n=277) compared to intraperitoneally (1.51 ± 0.29 h, n=134, $p < 0.001$, independent sample t-test). However, the route of administration was directly related to the use of anaesthesia, and all the animals injected with cisplatin intravenously (i.v.) had prior anaesthesia during which an i.v. line was implanted or were anaesthetised at the time of cisplatin injection, and prior anaesthesia was not reported in any of the animals that received an intraperitoneal (i.p.) injection of cisplatin. The recovery period between anaesthesia and the administration of cisplatin did not make a difference as ferrets that received cisplatin under anaesthesia developed emesis with a latency of 1.21 ± 0.32 h (n=93), and those allowed up to 3 and more than 3 days recovery developed emesis with a latency of 1.11 ± 0.31 h (n=51) and 1.13 ± 0.46 h (n=89), respectively (one-way ANOVA, $p = 0.21$). The use of an injectable anaesthetic (sodium pentobarbital 30-35 mg.kg⁻¹ i.p.) further shortened the latency (0.95 ± 0.14 h, n=46) compared to volatile anaesthetics (1.21 ± 0.39 h, n=176, $p < 0.001$, independent sample t-test). Intraperitoneal cisplatin induced a more severe emetic response and 156 ± 41 R+V (n=19) and 172 (n=65, SD not available) were quantified over 4h and 6h, respectively compared to 102 ± 52 R+V (n=180, $p < 0.001$, independent sample t-test) and 152

(n=8, SD not available) following i.v. cisplatin injection (with prior anaesthesia). No differences were observed over an observation period of 2h (i.p.: 72 ± 41 , n=22; i.v.: 88 ± 32 , n=18, $p=0.194$, independent samples t-test). There was not enough data available on the emetic response quantified for 3, 24 and 40h to investigate the influence of the mode of administration of cisplatin and the use of anaesthesia.

In animals that did not receive any vehicle, the latency was 1.39 ± 0.20 h (n=18) and ferrets had 92 ± 15 R+V (n=5). Different vehicles such as saline/distilled water (1.30 ± 0.38 h, n=296; 97 ± 31 R+V, n=125), propylene glycol (1.23 ± 0.06 h, n=4), PEG 300 (1.79 ± 0.18 h, n=5), Tween 80 (1.22 ± 0.19 h, n=8) and methyl cellulose (1.13 ± 0.25 h, n=5) impacted on the latency ($p<0.0001$, one-way ANOVA) but no significant differences were found compared to the group that received no vehicle ($p>0.05$, Bonferroni post-tests). Glucose (1.33 ± 0.24 h, n=7; 148 ± 100 R+V, n=7) was also found to increase the number of R+V ($p<0.05$, one-way ANOVA and Bonferroni post-tests).

No differences were detected in latency or number of R+V over 4h in groups of male ferrets only compared to groups of males and females ($p>0.05$, independent sample t-tests). The latency was significantly reduced in albino ferrets (1.07 ± 0.14 h, n=29) compared to fitch ferrets (1.34 ± 0.20 h, n=70) and mixed groups of albino and fitch ferrets (1.25 ± 0.36 h, n=108, $p<0.05$, one-way ANOVA and Bonferroni post-tests) but not enough data were available to compare the number of R+V.

The latency to the onset of emesis was significantly longer in ferrets bred in New Zealand (1.73 ± 0.37 h, n=11) compared to animals bred in the UK (1.25 ± 0.44 h, n=170) and in the USA (1.31 ± 0.19 h, n=176, $p<0.05$, one-way ANOVA and Bonferroni post-tests). No differences were detected in the number of R+V over 4h ($p>0.05$) but the number of R+V over 2h was reduced in New Zealand ferrets (40 ± 41 R+V, n=6) compared to U.K. animals (88 ± 32 R+V, n=18, $p=0.007$, independent sample t-tests). As all the ferrets originating from New Zealand were challenged with an intraperitoneal dose of cisplatin, a sub-analysis was carried out only in animals

administered cisplatin i.p. and the delay in latency was still significant in ferrets bred New Zealand compared to animals bred in the U.K. (1.43 ± 0.46 h, $n=29$, $p<0.05$) but not to animals bred in the U.S.A (1.51 ± 0.21 h, $n=84$, $p>0.05$, one-way ANOVA and Bonferroni post-tests).

The 5 mg.kg⁻¹ cisplatin model (acute and delayed emesis model)

Fourteen studies investigated cisplatin-induced acute and delayed emesis in the ferret; cisplatin was administered i.p. in all studies and no study reported prior use of anaesthesia. A biphasic profile of emesis was observed; the acute phase started 10.51 ± 0.58 h ($n=156$) after cisplatin administration, peaked after 12h and a nadir was reached after 24h (Figure 3B). The delayed phase was more intense than the acute phase and reached a peak 48h post cisplatin before gradually decreasing in intensity during the next 24h, until 72h post cisplatin, at which time a small amount of emesis still persisted. 105 ± 83 R+V ($n=215$) and 340 ± 171 ($n=153$) were observed during the acute and delayed phase, respectively (161 ± 98 R+V during day 2 and 179 ± 94 R+V during day 3, $n=130$). Overall, 448 ± 231 R+V ($n=153$) were observed during the entire 72h period.

In animals that did not receive any vehicle, the latency was 11.76 ± 9.86 h ($n=98$) and animals that received i.p. injections of vehicles such as saline, distilled water and 10% NaHCO₃ had a latency of 5.52 ± 3.32 h ($n=12$), 8.74 ± 8.61 h ($n=41$) and 5.71 ± 5.66 h ($n=5$), respectively. Overall the injection of a vehicle had an impact on the latency ($p<0.0001$, one-way ANOVA) but no specific differences were detected compared to the group that did not receive any vehicle ($p>0.05$, Bonferroni post-tests). None of the vehicles had a significant impact on the number of R+V during the acute or the delayed phase ($p>0.05$, one-way ANOVA). Neither the strain nor the sex of the ferrets had an impact on the latency or the number of R+V ($p>0.05$, one-way ANOVA).

Meta-analysis: the effect of anti-emetics

Effect of ondansetron on the acute phase of emesis

Outcome: number of retches and vomits (R+V)

Data for the number of R+V was extracted from 11 full papers, 23 comparisons involving 107 ferrets assessed the efficacy of ondansetron vs. control during the acute phase of emesis induced by 5 and 10 mg.kg⁻¹ cisplatin. As shown in Figure 4 the overall effect of ondansetron was a reduction of the R+V by about 70% (-0.69, -0.82 to -0.55) and this was highly significant (Z=10.05, p<0.0001). A small statistical heterogeneity was detected ($\chi^2=37.15$, df=23, p=0.03; I²=38.1%).

Five variants of the acute model of cisplatin-induced emesis were combined in this meta-analysis: emesis induced by 5 mg.kg⁻¹ cisplatin and R+V quantified for 24h and emesis induced by 10 mg.kg⁻¹ and R+V quantified for 24h, 6h, 4h and 2h.

Ondansetron significantly reduced the R+V in all variants of the model but one; as shown Table 3, the reduction of R+V did not reach statistical significance when emesis was induced by 10 mg.kg⁻¹ cisplatin and quantified for 24h. There was a trend for the effect of ondansetron to increase with shorter observation times (41, 68, 70 and 93% reduction for 24, 6, 4 and 2h observation periods, respectively) but this did not reach statistical significance. The R+V reduction was dose-dependent, doses of 1-10 mg.kg⁻¹ afforded a more effective protection than lower doses of 0.1-0.5 mg.kg⁻¹ (40% and 83%, respectively, Z=2.52, p=0.010). The regimen of ondansetron administration did not change the outcome; the effect of ondansetron was similar with i.v., i.p., and s.c. injections (Z tests, p>0.05) and ferrets treated 30 min prior to cisplatin administration received the same degree of protection as ferrets treated at the time of cisplatin injection (Z=0.04, p=0.965, see Table 3). With longer observation periods, ondansetron three times daily was as effective as twice-daily injections (Z=0.05, p=0.959). Ondansetron had the same efficacy on the R+V induced by an i.p. or an i.v. dose of cisplatin (Z=1.07, p=0.287) and the origin of the animals or the

quality score of the studies (see Table 1) did not influence the outcome (Z tests, $p>0.05$).

Outcome: number of animals with emesis

Data on the number of animals with emesis was extracted from 14 publications; 28 comparisons involving 256 ferrets were identified. The global estimate of the effect of ondansetron was -0.33 (-0.48 to 0.17) indicating that following the administration of cisplatin 5 or 10 mg.kg⁻¹, ondansetron abolished the emetic response during the observation time in one third of the ferrets (see Figure 5). Overall, this effect was significant (Z=4.09, $p<0.001$) but a substantial statistical heterogeneity ($\chi^2=115.13$, $df=27$, $p<0.001$, $I^2=76.5\%$) was detected between comparisons. Subgroup analyses revealed differences in estimates of efficacy between variants of the model. Whereas ondansetron had a significant effect against emesis induced by 10 mg.kg⁻¹ cisplatin and quantified over short observation times (2-4h) it did not show any significant effect against 10 mg.kg⁻¹ cisplatin-induced emesis quantified for 6 and 24h and 5 mg.kg⁻¹ cisplatin-induced emesis quantified for 24h (see Table 4). Efficacy increased as the dose increased, and only doses of ondansetron higher than 0.1 mg.kg⁻¹ had a significant effect but there was significant heterogeneity within those two subgroups (see Table 4). No statistical differences were detected between i.p., i.v. and oral (p.o.) administration of ondansetron (Z tests, $P>0.05$) but χ^2 and I^2 tests revealed a high degree of heterogeneity in all 3 groups. Administered s.c., ondansetron was ineffective but this could potentially be misleading as only 2 comparisons were included in that group and both reported the number of animals completely protected for 24h in which setting none of the animals were completely protected (see Table 4 and Figure 5). The regimen used did not influence significantly the number of animals completely protected by ondansetron. There were no differences between the subgroup that received ondansetron at the time of cisplatin injection and the subgroups that received it 30 min and 1h prior to cisplatin (Z-tests, $p>0.05$) but once again, these results should be taken with caution as the heterogeneity within each

subgroup was high. With longer observation times (24h), ondansetron was equally ineffective given 2 or 3 times a day. Ondansetron appeared slightly more effective when cisplatin was injected i.v. compared to i.p. but this did not reach statistical significance ($Z=1.757$, $p=0.079$) and could be biased by the fact that in all the comparisons where animals were observed for 24h, cisplatin was injected i.p. Furthermore, heterogeneity was, once again, highly significant in both groups (see Table 4). The origin of the animals and the quality score of the studies did not influence the effect of ondansetron (Z tests, $p>0.05$), however heterogeneity was high in all subgroups (see Table 4).

Outcome: latency

Latency data was extracted from 10 full papers. Fifteen comparisons involving 131 ferrets assessed the effect of ondansetron on emesis induced by 10 mg.kg^{-1} cisplatin and 3 comparisons assessed the effect of ondansetron on the latency to the onset of emesis induced by 5 mg.kg^{-1} cisplatin (see Figure 6). The global estimate of the effect of ondansetron on the latency was 0.86 (0.49-1.24), which means that the latency was nearly twice as long in the groups treated with ondansetron compared to the control groups. This effect was significant ($Z=4.45$, $p<0.001$) but χ^2 test revealed a high degree of heterogeneity ($\chi^2=314.35$, $df=14$, $p<0.001$), which was corroborated by the I^2 (96%). Subgroup analysis revealed that ondansetron statistically delayed the latency to the onset of emesis induced by 10 mg.kg^{-1} cisplatin but not 5 mg.kg^{-1} cisplatin (Table 5 and Figure 6). The effect of ondansetron was dose-dependant and doses of 1 mg.kg^{-1} conferred a significantly higher protection, increasing the latency by about 200% (Z tests, $p<0.05$). Ondansetron was more effective when given i.p. than p.o. or i.v. (Z tests, $p<0.05$); however, this result needs to be taken with caution as ondansetron was injected i.p. in all the comparisons where the highest dose was given (see Figure 6). No significant differences were observed with different treatment times, there was no difference in outcome if cisplatin was injected i.p. or i.v. and the origin of the ferrets did not influence the outcome (Z tests, $p>0.05$). The

outcome was not influenced by the quality of the study (see Table 1) as no differences were detected between studies scoring less than 5 out of 9, between 5 and 7/9 and 7.5 or higher (Z tests, $p > 0.05$).

Funnel plots for the effect of ondansetron on the R+V and the number of animals with emesis were relatively symmetrical (see Figure 7). The funnel plot for the latency was slightly asymmetrical, which reflects the high degree of heterogeneity detected for this outcome. Overall no associations between treatment effect and sample size were detected, suggesting no evidence of publication bias.

Effect of 5-HT₃ receptor antagonists on the latency to the onset of emesis induced by 10 mg.kg⁻¹ cisplatin.

The effects of 5-HT₃ receptor antagonists on the latency to the onset of 10 mg/kg cisplatin-induced emesis were investigated with 11 different anti-emetics (ondansetron, granisetron, tropisetron, indisetron, dolasetron, L-683,877, renzapride, zacopride, bemasetron, azasetron and ramosetron), this data was extracted from 22 studies; 76 comparisons were reported, involving 587 ferrets. However, for 14 comparisons, because only one animal developed emesis in the treatment group, the point estimate and confidence interval could not be computed and was therefore not included in the calculation of the effect estimate. Altogether, 5-HT₃ receptor antagonists increased the latency by 72% (effect estimate: 0.72, 95% CI: 0.56-0.87); this effect was highly significant ($Z=9.08$, $p < 0.0001$) but a high degree of heterogeneity ($\chi^2=1001.57$, $df=61$, $p < 0.0001$, $I^2=93.9\%$) was detected. Dolasetron (0.02, -0.76-0.80) renzapride (1.11, -0.18-2.40), bemasetron (0.29, -0.17-1.20) and ramosetron (0.19, -0.02-0.39) did not delay the onset of emesis in a statistically significant manner (Z-tests, $P > 0.05$) whereas ondansetron (0.88, 0.49-1.27), granisetron (0.67, 0.41-0.93), tropisetron (0.49, 0.17-0.81), indisetron (0.92, 0.28-1.57), L-683,877 (0.72, 0.11-1.33), zacopride (0.79, 0.37-1.20) and azasetron (0.52, 0.37-0.67) significantly increased the latency by 49-92% (Z-tests, $p < 0.05$).

Effect of 5-HT₃ receptor antagonists on the acute and delayed phases of emesis induced by 5 mg.kg⁻¹ cisplatin.

Data for the effects of 5-HT₃ receptor antagonists on the daily emetic response induced by 5 mg.kg⁻¹ i.p. cisplatin were extracted from 5 studies; 8 comparisons were identified, involving 72 animals. 5-HT₃ receptor antagonists reduced the number of R+V by 68% (-0.68, -0.91 to -0.45) on day 1, 67% (-0.67, -0.86 to -0.48) on day 2 and 53% (-0.53, -0.85 to -0.38) on day 3; this was statistically significant on each of the 3 days (Z=5.74, Z= 6.81 and Z=4.44 for day 1, 2 and 3 respectively; p<0.0001, see Figure 8). There was no difference between the effect of 5-HT₃ receptor antagonists on each of the 3 days (Z tests, P>0.05); no statistical heterogeneity was detected (χ^2 tests, p>0.05 and I²=0% on each of the 3 days). The effects of granisetron and ondansetron were significant for each of the 3 days, whereas indisetron did significantly reduce the R+V during day 1 and 3 but not day 2. No significant differences were detected between the effects of ondansetron, granisetron and indisetron for each of the 3 days (Z-tests, p>0.05).

DISCUSSION AND CONCLUSIONS

Cisplatin-induced emesis in the ferret

We found that the latency to the onset of the cisplatin-induced emesis was dose-dependent, which is consistent with findings in other species such as humans [71], dogs [10] and pigeons [106]. A step-change was observed between 5 and 6 mg.kg⁻¹, suggesting a difference in the mechanisms triggering emesis at low and high dose, possibly the activation of an additional mechanism (e.g. recruitment of less sensitive vagal afferent branches, area postrema). Prior anaesthesia and the route of administration of cisplatin were identified as confounding factors; the emetic response was also modulated by some of the vehicles used and factors inherent to the ferrets such as strain and origin. The difference between intravenous and intraperitoneal cisplatin may only reflect prior anaesthesia, as these two factors were dependent in the present study. Certainly, anaesthesia had an impact in its own right as differences were detected between injectable and volatile anaesthetics. The impact of the ferrets' origin could reflect a genuine difference between populations of ferrets but it might also indicate differences between laboratories rather than a difference between animals; this cannot be determined from the present study. These findings however stress the relevance of choosing appropriate controls (e.g. vehicle control, sham-operated) and homogeneous groups of animals when using the ferret cisplatin model of emesis.

The profile of emesis induced by 5 mg.kg⁻¹ i.p. cisplatin in the ferret was clearly biphasic, which is consistent with the profile of emesis observed in the clinic [84] but differences were observed in the timing and magnitude of the two phases. Whereas the acute phase is more severe than the delayed phase in humans [72, 84], with an onset 1-6h following cisplatin infusion [55, 71, 84], the latency to the onset of the acute phase was greater in the ferret (>10h) and its relative intensity compared to the delayed phase was lower. The incidence of emesis on each day could not be

investigated in the ferret as all reports stated that 100% of the animals developed an emetic response but no distinction was made between the acute and delayed phases. A few studies have however suggested that the acute phase was not observed in all animals [115, 147], which is also consistent with our recent observations [104] and suggests that whereas the incidence of emesis during the delayed phase is close to 100% the incidence of acute emesis at this dose is lower. In humans treated with placebo anti-emetics, however, the incidence of emesis during the acute phase [98%, 71] is higher than during the delayed phase (44-89% [43, 72]).

Effect of 5-HT₃ receptor antagonists

The efficacy of ondansetron in the acute model of cisplatin-induced emesis was assessed measuring 3 outcomes: the number of R+V, the number of animals with emesis and the latency to the onset of emesis. Overall, all 3 outcomes permitted the detection of significant anti-emetic protection, which is consistent with findings in humans [24], but different variants of the model resulted in different levels of anti-emetic protection. Whereas, all variants of the acute model reflected a similar reduction of R+V, ondansetron only delayed significantly the onset of emesis following 10 but not 5 mg.kg⁻¹ cisplatin, and the number of animals with emesis was only reduced with observation periods no longer than 4h. In the 10 mg.kg⁻¹ 4h variant of the model, half of the animals were completely protected from emesis, which was comparable to percentage of patients free of emesis during the acute phase of high dose (>50 mg.m⁻²) cisplatin-induced emesis in human patients [58, 65, 85, 124]. Overall the acute phase of emesis induced by 5 mg.kg⁻¹ cisplatin represented poorly the clinical situation and the 4h-10 mg.kg⁻¹ model was more predictive of cisplatin-induced emesis in humans.

Overall, 5-HT₃ receptor antagonists reduced the emetic response to the same extent during the acute and delayed phases, which contrasts with findings reported in the

majority of clinical studies, describing limited or non significant effect of 5-HT₃ receptor antagonists during the delayed phase [57, 73]. This discrepancy may be explained by a difference in outcome usually measured in humans (daily incidence, percentage of patients developing emesis) and ferrets (severity, number of R+V). Even though daily incidence and severity (measured by visual analogue scale) of the delayed phase emesis appear to be positively correlated in the absence of anti-emetic therapy [72], they can be uncoupled following anti-emetic treatment and the number of emetic episodes may be reduced while the incidence remains unchanged [100]. Alternatively, it is conceivable that the delayed phase of emesis in the ferret is more sensitive to 5-HT₃ receptor antagonists than it is in humans. The latter would be consistent with a longer acute phase in the ferret [see 110 for details], implying that the mechanism regulating the acute phase (i.e. 5-HT-mediated activation of the abdominal vagal afferents) remains activated longer. The ferret model thus correctly identified the anti-emetic potential of 5-HT₃ receptor antagonists against both the acute and delayed phases of cisplatin-induced emesis but the magnitude of the anti-emetic effect during the delayed phase appears greater in the ferret than it is in humans.

Methodology

In the present study, the methodology used in the meta-analysis of human clinical trials was modified and adapted to animal research, and several concessions had to be made. First of all, the criteria used to select studies for inclusion into the systematic review and meta-analysis, and assess quality, did not include randomization and blinding. Whereas these two parameters are considered essential for human clinical trials and it has been suggested that their absence favours positive findings in animal research [8], emesis is an objective measurement, which is not investigator-dependent and we have no reason to believe that the inclusion of such studies in our analysis biased our findings. Additionally, randomization and blinding in

the identified studies were too rarely reported to be used as inclusion criteria. The exclusion criteria were chosen to ensure the collection of reliable, clearly defined data. The majority of excluded studies (see Table 2) were removed because emesis was not quantified as latency, retches, vomits and/or incidence. We chose not to include outcomes such as “emetic episodes” or “bouts of emesis” in the present analysis because of the disparity of definitions and possible interpretations. This may however restrict the conclusions of our study.

Secondly, whereas clinical trials usually reports tens or hundreds of patients in each study arm, we found that in the cisplatin ferret model, typically 4 to 8 animals were allocated in each treatment group. This may limit the relevance of such an analysis, designed to compare much bigger samples. Additionally, because a majority of studies compared one control group to several treatment groups—typically different doses of a compound—in order to maintain the data from different doses as distinct comparisons, the number of animals in the control group was divided by the number of treatment groups it was compared to. The limitation of such an approach is that in the effect estimate calculation, the weight of such comparisons is reduced, which benefits comparisons extracted from studies that only compared one control group to one treatment group and is not justified by the quality of the studies.

Conclusions

We demonstrated the potential of a meta-analysis to address the 3R's (Replacement, Refinement and Reduction), developed by Russel and Burch as criteria for a humane use of animals in research [126]. By maximising the utilisation of animal data, thus extracting novel scientific information without increasing the number of animals, such analysis addresses Reduction, as this reduces the future use of animals. Additionally, the effects of ondansetron on the 3 outcomes highlighted a logical Refinement of the model by reducing the observation period. The cisplatin 10 mg/kg-4h variant of the model stands out as the most appropriate to study the acute phase of cisplatin-

induced emesis, whereas 5 mg/kg-24 to 72h remains the model of choice to study cisplatin-induced delayed emesis.

The present study is a proof of concept. In an attempt to focus the scope of the analysis, it was limited to an animal model with one emetic: cisplatin, one species: the ferret and one class of anti-emetic drugs: 5-HT₃ receptor antagonists; the drugs investigated are already successfully used in humans against chemotherapy-induced emesis. Globally, the effects in the ferret were consistent with clinical findings, which was expected as they were originally developed in the ferret model; this demonstrates that a meta-analysis is an appropriate method to identify the anti-emetic potential of a drug and confirms that the ferret model of cisplatin-induced emesis is truly predictive and relevant to humans. This method can now be applied to investigate the effects of NK₁ receptor antagonists, which were also developed using the ferret and which have recently been introduced into the clinic. However, recent studies suggest that there may be a discrepancy between the “broad spectrum” anti-emetic efficacy in the ferret and the efficacy in the clinic [3, 25]. This method can also be used in other “model” species (e.g. dog) to reassess “older” compounds such as dopamine receptor antagonists or opioids, whose effects on cisplatin-induced emesis are less well characterized. It can also be directly applied to other emetic models (different emetogen and/or different species) and adapted to assess the relevance of models arguably predictive of nausea and emesis such as pica in the rat and conditioned taste aversion [2, 77].

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FIGURE LEGENDS

Figure 1. Flow chart of identified studies. Reproduced and adapted from the QUOROM statement flow diagram [97].

Figure 2. Latency to the onset of emesis (first retch, vomit or vomiting episode) induced by various doses of cisplatin. Data collected from 64 studies involving 702 animals and plotted on the graph as weighted mean \pm SD. Differences between the doses were assessed by one-way ANOVA followed by Bonferroni post-tests, *** $p < 0.0001$ compared with all other doses in the post-tests. The exact latency values, the number of ferrets from which those values were calculated (n) and the number of studies from which this data was extracted (S) are given above each column.

Figure 3. Profile of emesis induced by 10 mg.kg⁻¹ (A) and 5 mg.kg⁻¹ (B) cisplatin in the ferret. A: data plotted as mean vomits \pm SD per 30 min periods, collected from 6 studies involving 34 animals and mean retches \pm SD, collected from 4 of those studies involving 20 out of the 34 animals. B: Data plotted as weighted mean R+V \pm SD per 4h periods collected from 9 studies involving 92 animals.

Figure 4. Efficacy of ondansetron number of retches + vomits during the acute phase of emesis induced by cisplatin 5 or 10 mg.kg⁻¹. Point estimates and 95% confidence intervals for each of the ondansetron vs. control comparisons ranked by dose. The effect estimate was computed as the weighted mean difference (WMD) and expressed as the proportion of retches and vomits in the control group. An effect estimate of -1 indicates that emesis was abolished in the treatment group, 0 indicates that the treatment had no effect on the R+V response and an effect estimate > 0

indicates that the treatment increased the number of R+V. The size of each square represents the weight of the comparison in the WMD calculation

Figure 5. Efficacy of ondansetron on the number of animals developing an acute phase of emesis following cisplatin 5 or 10 mg.kg⁻¹. Point estimates and 95% confidence intervals for each of the ondansetron vs. control comparisons ranked by dose. The effect estimate was computed as the risk difference (RD) and represents the proportion of animals with emesis during the duration of the observation period. An effect estimate of 0 indicates that the treatment had no effect on the number of animals with emesis, -1 indicates maximal effect. The size of each square represents the weight of the comparison in the total RD calculation.

Figure 6: Efficacy of ondansetron on the latency to emesis induced by cisplatin (5 or 10 mg.kg⁻¹). Point estimates and 95% confidence intervals for each of the ondansetron vs. control comparisons ranked by dose. The effect estimate is the impact of the treatment on the latency expressed as a proportion of the latency in the control group. An effect estimate <0 indicates that the latency was shorter in the control group than in the treatment group, 0 indicates that the treatment had no effect on the latency and an effect estimate of 1 indicates that the treatment increased the latency by 100%. The size of each square represents the weight of the comparison in the WMD calculation. Note that in 3 comparisons, the effect estimate was not estimable as only one animal developed emesis in the group treated with ondansetron.

Figure 7: Funnel plots for the effect of ondansetron on the number of retches + vomits (A), number of animals with emesis (B) and latency (C). For each comparison, the effect estimates are plotted on the x-axis and corresponding standard errors are plotted on the y-axis.

Figure 8: Efficacy of 5-HT₃ receptor antagonists on the daily number of retches + vomits (R+V) induced by 5 mg.kg⁻¹ i.p. cisplatin during the acute (day 1) and delayed (days 2 and 3) phases of emesis. Point estimates and 95% confidence intervals for each of the 5-HT₃ receptor antagonist vs. control comparisons ranked by dose. The effect estimate was computed as the weighted mean difference (WMD) and expressed as the proportion of retches and vomits in the control group. An effect estimate of -1 indicates that emesis was abolished in the treatment group, 0 indicates that the treatment had no effect on the R+V response and an effect estimate >0 indicates that the treatment increased the number of R+V. The size of each square represents the weight of the comparison in the WMD calculation

Table 1. List of 68 included publications.

Study	Quality score	Cisplatin dose	Obs. period	Study	Quality score	Cisplatin dose	Obs. period
Angel <i>et al.</i> , 1993 [4]	7	10 mg.kg ⁻¹ , i.v.	3h	Minami <i>et al.</i> , 1998 [91]	6	10 mg.kg ⁻¹ , i.p.	6h
Barnes <i>et al.</i> 1987 [6]	6	10 mg.kg ⁻¹ , i.v.	4h	Miner <i>et al.</i> , 1986a [94]	4	10 mg.kg ⁻¹ , i.v.	4h
Barnes <i>et al.</i> , 1988 [5]	9	10 mg.kg ⁻¹ , i.v.	3h	Miner <i>et al.</i> , 1987 [96]	4	10 mg.kg ⁻¹ , i.v.	4h
Barnes <i>et al.</i> , 1991 [7]	7	10 mg.kg ⁻¹ , i.v.	4h	Nakayama <i>et al.</i> , 2005 [99]	8.5	5, 10 mg.kg ⁻¹ , i.p.	24h, 4h
Bermudez <i>et al.</i> , 1988 [9]	4.5	10 mg.kg ⁻¹ , i.v.	4h	Ozaki and Sakamoto, 1999 [103]	7	10 mg.kg ⁻¹ , i.v.	4h
Bingham <i>et al.</i> , 1994 [11]	4.5	12.5 mg.kg ⁻¹ , i.v.	4h	Reynolds <i>et al.</i> , 1991 [108]	6	10 mg.kg ⁻¹ , i.p.	3h
Blower, 1990 [12]	6	10 mg.kg ⁻¹ , i.v.	4h	Rudd <i>et al.</i> , 1992 [111]	5	10 mg.kg ⁻¹ , i.v.	4h
Costall <i>et al.</i> , 1986 [21]	7	10 mg.kg ⁻¹ , i.v.	2h	Rudd <i>et al.</i> , 1994a [114]	6.5	10 mg.kg ⁻¹ , i.p.	40h
Costall <i>et al.</i> , 1987b [19]	6	10 mg.kg ⁻¹ , i.v.	2h	Rudd and Naylor, 1994b [117]	5	5, 10 mg.kg ⁻¹ , i.p.	24h
Costall <i>et al.</i> , 1987c [22]	6.5	10, 15 mg.kg ⁻¹ , i.v.	2h	Rudd and Naylor, 1994c [118]	6	10 mg.kg ⁻¹ , i.v.	4h
Costall <i>et al.</i> , 1990a [20]	7	10, 15 mg.kg ⁻¹ , i.v.	4h	Rudd <i>et al.</i> , 1996b [115]	7.5	5, 10 mg.kg ⁻¹ , i.p.	24h, 40h
Costall <i>et al.</i> , 1990b [23]	7	10 mg.kg ⁻¹ , i.v.	4h	Rudd and Naylor, 1996c [119]	7.5	5 mg.kg ⁻¹ , i.p.	24h
Davis, 1988 [26]	8	10, 12, 20 mg.kg ⁻¹ , i.v.	2h	Rudd <i>et al.</i> , 1996a [112]	8	10 mg.kg ⁻¹ , i.v.	4h
Delagrangre <i>et al.</i> , 1996 [26, 27]	3.5	10 mg.kg ⁻¹ , i.p.	5h	Rudd and Naylor, 1997 [120]	8.5	10 mg.kg ⁻¹ , i.p.	24h
Endo <i>et al.</i> , 1990b [33]	6	7, 10 mg.kg ⁻¹ , i.p.	6h	Rudd <i>et al.</i> , 1998b [113]	5.5	10 mg.kg ⁻¹ , i.p.	24h
Endo <i>et al.</i> , 1994 [36]	6.5	10 mg.kg ⁻¹ , i.p.	6h	Rudd <i>et al.</i> , 2006a [122]	6	10 mg.kg ⁻¹ , i.p.	6h
Fink-Jensen 1992 [38]	5	10 mg.kg ⁻¹ , i.v.	4h	Rycroft <i>et al.</i> , 1996 [127]	5	10 mg.kg ⁻¹ , i.v.	4h
Florczyk <i>et al.</i> , 1982 [40]	5	6, 8, 10 mg.kg ⁻¹ , i.v.	4h	Sam <i>et al.</i> , 2001 [128]	7.5	5 mg.kg ⁻¹ , i.p.	24h
Fukunaka <i>et al.</i> , 1998 [42]	8	5 mg.kg ⁻¹ , i.p.	24h	Sam <i>et al.</i> , 2003 [129]	7.5	5 mg.kg ⁻¹ , i.p.	24h
Gonsalves <i>et al.</i> , 1996 [47]	7.5	10 mg.kg ⁻¹ , i.p.	2h	Sam <i>et al.</i> , 2007 [130]	7.5	5 mg.kg ⁻¹ , i.p.	24h
Gyllys <i>et al.</i> , 1988 [49]	5	12 mg.kg ⁻¹ , i.v.	4h	Schurig <i>et al.</i> , 1982 [131]	5.5	8 mg.kg ⁻¹ , i.p.	4h
Haga <i>et al.</i> , 1993 [50]	4.5	8 mg.kg ⁻¹ , i.v.	5h	Shiroshita <i>et al.</i> , 1993 [132]	6	10 mg.kg ⁻¹ , i.p.	6h
Hawthorn <i>et al.</i> , 1988 [56]	8.5	10 mg.kg ⁻¹ , i.p.	4h	Singh <i>et al.</i> , 1997 [134]	4.5	5 mg.kg ⁻¹ , i.p.	24h
Higgins <i>et al.</i> , 1989 [59]	5.5	9 mg.kg ⁻¹ , i.p.	3h	Taniguchi <i>et al.</i> , 2004 [137]	5	5 mg.kg ⁻¹ , i.p.	24h
Kamato <i>et al.</i> , 1991 [67]	6.5	10 mg.kg ⁻¹ , i.v., i.p.	4h	Tattersall <i>et al.</i> , 1992 [139]	7.5	10 mg.kg ⁻¹ , i.v.	4h
Kamato <i>et al.</i> , 1993 [66]	6.5	10 mg.kg ⁻¹ , i.v.	6h	Tattersall <i>et al.</i> , 1993 [142]	5.5	10 mg.kg ⁻¹ , i.v.	4h
King and Sanger, 2005 [70]	7.5	10 mg.kg ⁻¹ , i.p.	6h	Tattersall <i>et al.</i> , 2000 [140]	3.5	5, 10 mg.kg ⁻¹ , i.p., i.v.	24h, 4h
Lau <i>et al.</i> , 2005 [75]	7.5	10 mg.kg ⁻¹ , i.p.	2h	Tsuchiya <i>et al.</i> , 2002 [144]	7.5	5 mg.kg ⁻¹ , i.p.	24h
Lehmann and Karrberg, 1996 [76]	7.5	10 mg.kg ⁻¹ , i.v.	3h	Watson <i>et al.</i> , 1995 [148]	7.5	10 mg.kg ⁻¹ , i.p.	2h
Marr <i>et al.</i> , 1992 [81]	6.5	10 mg.kg ⁻¹ , i.v.	4h	Yamakuni <i>et al.</i> , 2002 [150]	5	5, 10 mg.kg ⁻¹ , i.p.	24h, 4h
Marr <i>et al.</i> , 1994a [82]	7	10 mg.kg ⁻¹ , i.v.	4h	Yamakuni <i>et al.</i> , 2006 [149]	7.5	5, 10 mg.kg ⁻¹ , i.p., i.v.	24h, 4h
Marr <i>et al.</i> , 1994b [83]	3.5	12.5 mg.kg ⁻¹ , i.v.	4h	Yoshida <i>et al.</i> , 1992a [151]	4	10 mg.kg ⁻¹ , i.v.	3h
Miller <i>et al.</i> , 1993 [90]	7	10 mg.kg ⁻¹ , i.v.	4h	Yoshida <i>et al.</i> , 1993 [153]	4.5	10 mg.kg ⁻¹ , i.v.	3h
Minami <i>et al.</i> , 1997 [93]	6	10 mg.kg ⁻¹ , i.p.	6h	Yoshikawa <i>et al.</i> , 2001b [157]	3.5	10 mg.kg ⁻¹ , i.v.	4h

For each included study, the quality score (out of 9), the dose and mode of administration of cisplatin and the duration of the acute phase

observation period are indicated.

Table 2. List of 47 excluded publications.

Study	Reason for exclusion	Study	Reason for exclusion	Study	Reason for exclusion
Blum <i>et al.</i> , 1992 [13]	emesis	Gooch <i>et al.</i> 1998 [48]	anaesthesia	Rudd <i>et al.</i> , 2001 [116]	group number
Bountra <i>et al.</i> , 1993 [15]	emesis	Haga <i>et al.</i> , 2000 [51]	emesis	Rudd <i>et al.</i> , 2006b [123]	duplicate
Chevalier <i>et al.</i> , 1998 [16]	emesis	Hale <i>et al.</i> , 1998 [53]	duplicate	Rupniak <i>et al.</i> , 1997 [125]	emesis
Clark <i>et al.</i> , 1993 [17]	duplicate	Hale <i>et al.</i> , 2000 [52]	duplicate	Shiroshita <i>et al.</i> , 1992 [133]	emesis
Costall <i>et al.</i> , 1987a [18]	duplicate	Hargreaves <i>et al.</i> , 1994 [54]	duplicate	Stables <i>et al.</i> , 1987 [136]	duplicate
Eglen <i>et al.</i> , 1993 [31]	emesis	Hollingworth <i>et al.</i> , 2006 [60]	group number	Tattersall <i>et al.</i> , 1990 [138]	duplicate
Eglen <i>et al.</i> , 1994 [29]	emesis	Ito <i>et al.</i> , 1990 [64]	emesis	Tattersall <i>et al.</i> , 1996 [141]	group number
Eglen <i>et al.</i> , 1995 [30]	emesis	Kim <i>et al.</i> , 2005 [69]	emesis	Twissell <i>et al.</i> , 1993 [145]	duplicate
Endo <i>et al.</i> , 1990a [32]	duplicate	Lasheras <i>et al.</i> , 1996 [74]	emesis	Van Sickle <i>et al.</i> , 2003 [146]	emesis
Endo <i>et al.</i> , 1992 [34]	group number	Matsui <i>et al.</i> , 1992 [86]	emesis	Yoshida <i>et al.</i> , 1991 [154]	emesis
Endo <i>et al.</i> , 1995 [35]	emesis	Minami <i>et al.</i> , 1991 [92]	duplicate	Yoshida <i>et al.</i> , 1992b [152]	emesis
Fitzpatrick <i>et al.</i> , 1990 [39]	emesis	Miner <i>et al.</i> 1986b [95]	duplicate	Yoshikawa <i>et al.</i> , 1996 [155]	emesis
Florczyk, <i>et al.</i> , 1981 [41]	duplicate	Monkovic <i>et al.</i> , 1988 [98]	emesis	Yoshikawa <i>et al.</i> , 2001a [156]	emesis
Gardner <i>et al.</i> 1994 [45]	emesis	Ohta <i>et al.</i> , 1996 [102]	emesis	Youssefyeah <i>et al.</i> , 1992a [159]	duplicate
Gardner <i>et al.</i> 1995 [46]	emesis	Price <i>et al.</i> , 1990 [107]	emesis	Youssefyeah <i>et al.</i> , 1992b [158]	duplicate
Gardner <i>et al.</i> 1996 [44]	emesis	Rudd <i>et al.</i> , 1998a [121]	emesis		

Reason for exclusion is indicated as: duplicate: data published elsewhere; group number: number of animals in the group missing; emesis: emesis not quantified as number of animals free of emesis, number of retches, number of vomits or latency, or emesis not defined; anaesthesia: emetic response investigated in anaesthetized animals.

Table 3. Sensitivity analyses of the effect of ondansetron on the number of retches + vomits (R+V) induced by cisplatin (5 or 10 mg.kg⁻¹).

	Effect estimate (proportion of R+V difference)	95% CI	Number of comparisons	Overall effect (Z tests)	Heterogeneity (χ^2)
Cisplatin dose and duration of the observation period					
5 mg/kg (24h)	-0.61	-0.87 to -0.35	5	p<0.001***	p=0.800
10 mg/kg (24h)	-0.41	-0.95 to 0.13	4	p=0.13	p=0.004**
10 mg/kg (6h)	-0.68	-1.09 to -0.26	3	p=0.001**	p=0.140
10 mg/kg (4h)	-0.70	-0.94 to -0.46	8	p<0.001***	p=0.100
10 mg/kg (2h)	-0.93	-1.15 to -0.70	4	p<0.001***	p=0.750
Ondansetron dose					
0.01 mg.kg ⁻¹	-0.71	-1.16 to -0.26	1	p=0.002**	N/A
0.1-0.5 mg.kg ⁻¹	-0.40	-0.69 to -0.10	8	p=0.009**	p=0.030*
1-10 mg.kg ⁻¹	-0.83	-0.95 to -0.70	15	p<0.001***	p=0.600
Mode of delivery of ondansetron					
i.v.	-0.77	-0.95 to -0.60	11	p<0.001***	p=0.130
i.p.	-0.59	-0.81 to -0.37	11	p<0.001***	p=0.030*
s.c.	-0.74	-1.45 to -0.03	2	p=0.040*	p=0.710
Treatment time					
With cisplatin	-0.67	-0.86 to -0.48	15	p<0.001***	p=0.010*
30 min before	-0.68	-1.09 to -0.26	3	p=0.001**	p=0.140
Twice daily	-0.74	-1.45 to -0.03	4	p=0.04*	p=0.710
Three times daily	-0.72	-0.98 to -0.48	2	p<0.001***	p=0.26
Mode of administration of cisplatin					
i.v.	-0.77	-0.97 to -0.57	9	p<0.001***	p=0.100
i.p.	-0.62	-0.81 to -0.44	15	p<0.001***	p=0.080
Animal origin					
U.K.	-0.70	-0.88 to -0.53	15	p<0.001***	p=0.020*
U.S.A.	-0.67	-0.91 to -0.44	7	p<0.001***	p=0.330
N.Z.	-1.00	-0.83 to -0.17	1	p=0.020*	N/A
Quality score					
Less than 5/9	-0.65	-0.95 to -0.34	5	p<0.001***	p=0.060
5 to 7/9	-0.76	-0.97 to -0.56	9	p<0.001***	p=0.260
7.5 to 9/9	-0.65	-0.88 to -0.42	10	p<0.001***	p=0.050

The effect estimate was computed as the weighted mean difference (WMD) and expressed as the proportion of retches and vomits in the control group. An effect estimate of -1 indicates that emesis was abolished in the treatment group, 0 indicates that the treatment had no effect on the R+V response and an effect estimate >0 indicates that the treatment increased the number of R+V. The variables examined were the variant of the cisplatin model (5 or 10 mg.kg⁻¹ cisplatin and the duration of the observation period), the mode of administration of cisplatin, the dose of ondansetron, the regimen of ondansetron administration (mode of delivery and timing

relative to cisplatin administration), the animal origin (country animals were bred) and the quality score assigned to the study where comparisons were extracted.

Table 4. Sensitivity analyses of the effect of ondansetron on the number of animals with emesis following the administration of cisplatin (5 or 10 mg.kg⁻¹).

	Effect estimate (proportion of ferrets with emesis)	95% CI	Number of comparisons	Overall effect (Z tests)	Heterogeneity (χ^2)
Cisplatin dose and duration of the observation period					
5 mg/kg (24h)	0.00	-0.15- to 0.15	5	p=1.000	p=1.000
10 mg/kg (24h)	0.00	-0.23 to 0.23	4	p=1.000	p=1.000
10 mg/kg (6h)	-0.11	--0.38 to 0.15	3	p=0.400	p=0.280
10 mg/kg (4h)	-0.48	-0.70 to -0.26	12	p<0.001***	p<0.001***
10 mg/kg (2h)	-0.76	-1.21 to -0.31	4	p=0.001**	p=0.002**
Ondansetron dose					
0.01-0.03 mg.kg ⁻¹	-0.13	-0.37 to 0.12	4	p=0.31	p=0.93
0.1-0.5 mg.kg ⁻¹	-0.39	-0.68 to -0.11	10	p=0.006**	p<0.001***
1-10 mg.kg ⁻¹	-0.33	-0.57 to -0.10	14	p=0.006**	p<0.001***
Mode of delivery of ondansetron					
i.v.	-0.49	0.25-0.73	12	p<0.001***	p<0.001***
i.p.	-0.14	-0.10-0.38	11	p=0.25	p<0.001***
s.c.	-0.00	-0.27-0.27	2	p=1.000	p=1.000
p.o.	-0.64	-1.16 to -0.11	3	p=0.020*	p=0.020*
Treatment time					
With cisplatin	-0.43	-0.68 to -0.18	13	p<0.001***	p<0.001***
30 min before	-0.29	-0.60 to 0.02	6	p=0.060	p=0.020*
1h before	-0.64	-1.16 to -0.11	3	p=0.020*	p=0.020*
Twice daily	0.00	-0.27 to 0.27	2	p=1.000	p=1.000
Three times daily	0.00	-0.16 to 0.16	4	p=1.000	p=1.000
Mode of administration of cisplatin					
i.v.	-0.49	-0.73 to -0.25	12	p<0.001***	p<0.001***
i.p.	-0.21	-0.41 to -0.01	16	p=0.04*	p<0.001***
Animal origin					
U.K.	-0.24	-0.43 to -0.04	14	p=0.020*	p<0.001***
U.S.A.	-0.36	-0.57 to -0.14	13	p=0.001**	p<0.001***
N.Z.	1.00	-1.27 to -0.73	1	p<0.001***	N/A
Quality score					
Less than 5/9	-0.23	-0.62 to 0.16	3	p=0.250	p=0.030*
5 to 7/9	-0.44	-0.66 to -0.22	15	p<0.001***	p<0.001***
7.5 to 9/9	-0.18	-0.46 to 0.09	10	p=0.19	p<0.001***

The effect estimate was computed as the risk difference (RD) and represents the proportion of animals with emesis during the duration of the observation period. An effect estimate of 0 indicates that the treatment had no effect on the number of animals with emesis, -1 indicates maximal effect. The variables examined were the variant of the cisplatin model (5 or 10 mg.kg⁻¹ cisplatin and the duration of the observation period), the mode of administration of cisplatin, the dose of ondansetron, the regimen of ondansetron administration (mode of delivery and timing relative to

cisplatin administration), the animal origin (country animals were bred) and the quality score assigned to the study where comparisons were extracted.

Table 5. Sensitivity analyses of the effect of ondansetron on the latency to the onset of emesis induced by cisplatin (5 or 10 mg.kg⁻¹).

	Effect estimate (proportion of latency change)	95% CI	Number of comparisons	Overall effect (Z tests)	Heterogeneity (χ^2)
Cisplatin dose					
10 mg.kg ⁻¹	0.88	0.49-1.27	15	p<0.001***	p<0.001***
5 mg.kg ⁻¹	0.60	-0.97-2.16	3	p=0.45	p=0.29
Ondansetron dose					
0.01-0.02 mg.kg ⁻¹	0.36	0.00-0.72	3	p=0.050	p=0.008**
0.03-0.06 mg.kg ⁻¹	0.85	0.30-1.40	3	p=0.002**	p<0.001***
0.1 mg.kg ⁻¹	0.49	0.31-0.67	5	p<0.001***	p=0.140
1 mg.kg ⁻¹	1.96	1.66-2.25	7	p<0.001***	p=0.27
Mode of delivery of ondansetron					
i.v.	0.60	0.35-0.85	9	p<0.001***	p<0.001***
p.o.	0.34	0.15-0.53	2	p<0.001***	N/A
i.p.	1.54	0.67-2.41	5	p<0.001***	p<0.001***
s.c.	0.36	-0.94-1.65	2	p=0.59	p=0.31
Treatment time					
With cisplatin	0.62	0.34-0.68	6	p<0.001***	p=0.010*
20-30 min before	1.11	0.25-1.96	5	p=0.010**	p<0.001***
1h before	0.34	0.15-0.53	2	p=0.010**	N/A
30 min before and 45 min after	0.94	-0.01-1.89	2	p=0.050*	p<0.001***
Twice daily	0.36	-0.94-1.65	2	p=0.590	p=0.310
Three times daily	5.83	-3.02-14.68	1	p=0.020*	N/A
Mode of administration of cisplatin					
i.v.	0.60	0.35-0.85	9	p<0.001***	p<0.001***
i.p.	1.16	0.35-1.96	9	p=0.005	p<0.001***
Animal origin					
U.K.	0.76	0.44-1.07	5	p<0.001***	p=0.19
U.S.A.	0.86	0.39-1.33	13	p<0.001***	p<0.001***
Quality score					
Less than 5/9	0.94	-0.01-1.89	2	p=0.050	p<0.001***
5 to 7/9	0.63	0.32-0.94	11	p<0.001***	p<0.001***
7.5 to 9/9	1.42	0.31-2.53	5	p=0.01**	p<0.001***

The effect estimate was computed as the weighted mean difference (WMD) and represents the impact of the treatment on the latency expressed as a proportion of the latency in the control group. An effect estimate <0 indicates that the latency was shorter in the control group than in the treatment group, 0 indicates that the treatment had no effect on the latency and an effect estimate of 1 indicates that the treatment increased the latency by 100%. The variables examined were the dose and mode of administration of cisplatin, the dose of ondansetron, the regimen of ondansetron administration (mode of delivery and timing relative to cisplatin administration), the

animal origin (country animals were bred) and the quality score assigned to the study where comparisons were extracted.









