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Tolerance and Addiction; the patient, the parent or the clinician?

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TITLE PAGE**Tolerance and Addiction; the patient, the parent or the clinician?****Running Title:**

Tolerance and Addiction

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SUMMARY

Tolerance has been recognised for some time where chronic exposure to certain drugs, particularly benzodiazepines and opioids, is associated with apparent tachyphylaxis. When these drugs are stopped or progressively reduced as in 'tapering', withdrawal symptoms result. Tolerance and the flip-side of the coin, withdrawal, are the determinants of addiction. It is increasingly apparent that tolerance can occur acutely, even within the time span of a single anesthetic for a surgical procedure.

Addiction is caused by agents, foreign to the body, that provoke adaptation by homeostatic biological processes. When these agents are withdrawn the adaptive mechanisms, devoid of substrate, take time to diminish and produce symptoms recognisable under the term of 'withdrawal'.

Children may be exposed to these agents in different ways; in utero, as a result of substances that the mother ingests by enteral, parenteral or inhalational means that are transmitted to the infant via the placenta; as a result of an anaesthetic for surgery; or as a result of sedation and analgesia administered to offset the stresses and trauma inherent from intensive care treatment in the NICU or PICU.

Additionally, anesthetic and intensive care staff are exposed to powerful and addictive drugs as part of everyday practice, not simply by overt access, but also by subliminal environmental exposure.

Keywords:

Tolerance, addiction, withdrawal, neonatal abstinence, anesthesiology, intensive care.

Introduction

The drugs most commonly associated with tolerance in anesthesia and critical care are opioids and benzodiazepines. Opioids are the mainstay of intraoperative analgesia for procedures that do not lend themselves to regional neural blockade and both classes of drugs are the most prevalent agents in use for sedation and analgesia in pediatric critical care (1). Whereas withdrawal phenomena on cessation of these agents in critical care have been recognised for some considerable time (2, 3), their role in acute tolerance within the time-frame of pediatric surgery is becoming increasingly appreciated (4-9). Equally, tolerance and withdrawal phenomena have been reported with many different agents such as isoflurane (2), propofol (10, 11), barbiturates (12) and more recently dexmedetomidine (13) and clonidine (14).

What causes tolerance?

This is best described with opioid biology where there is a complex interplay of local intracellular mechanisms and neural pathways that interact with the transmission of pain impulses affecting the response at cellular level. Opioid receptors act in the modulation of pain sensation in sites such as cerebral cortex layers III and IV, thalamic nuclei, peri-aqueductal grey matter, corpus striatum and dorsal horn laminae I and II. These neuronal cells have bi-modal opioid receptors, capable of releasing stimulatory messenger protein G_s (hyperalgesia) or inhibitory messenger proteins, G_0 or G_i (analgesia). At adequate dosage opioids bind with receptors to release inhibitory G protein transmitters that decrease intracellular cyclic AMP (cAMP) and neuronal nitric oxide synthetase so resulting in analgesia. However, opioids can also produce hyperalgesia and this depends on the effect of the molecule at the receptor and whether this may release stimulatory G_s proteins (15).

Tolerance develops as a result of adaptation to the presence of opioids binding to receptors and the resultant biochemical changes in the cell. Receptors have been observed to internalize into the cell wall (desensitization) or decrease in number (down-regulation). Up-regulation of intracellular adenylyl cyclase production of cAMP can occur, as can increased release of dynorphins from descending spinal

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3 pathways that produce hyperalgesia by negative feedback (4, 15). Opioids vary in their structure and
4
5 their specific actions on opioid receptors and subsequent release of intracellular transmitters. In part
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7 this explains their variable potential for producing analgesia and also tolerance.
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9

10
11 Many cells with opioid receptors also contain N-methyl-D-aspartate (NMDA) receptors, which if
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13 activated, cause increased intracellular calcium and hyperalgesia. Opioids may activate
14
15 antinocioceptive but also pronocioceptive systems, such as these NMDA receptors, and these seem to
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17 have longer duration of action (15-17). Theoretically therefore, NMDA receptor antagonists such as
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19 ketamine may be expected to inhibit this pronocioceptive system, and this has been observed to be the
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21 case with production of analgesia at concentrations of ketamine below that which would produce
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23 analgesia by independent action. This has been exploited clinically as indicated below (17).
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29 **Acute Tolerance with Opioids**

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31
32 The development of acute tolerance (or tachyphylaxis) to opioids is well recognised (8). **Acute**
33
34 **tolerance to the analgesic effects of infusions of remifentanyl developed within 90-120 minutes in**
35
36 **human adult volunteers (9).** However, sedative tachyphylaxis was not similarly noted thus raising the
37
38 possibility that administration of larger doses to achieve analgesic effects may lead to increased
39
40 sedation and respiratory depression. There is also evidence that increasing the dose of remifentanyl
41
42 leads to increasing tolerance. In adult abdominal surgery, where the remifentanyl dose was kept
43
44 constant and desflurane titrated against patient autonomic response, the morphine needed
45
46 postoperatively was significantly less than in the comparator group where the desflurane was held at
47
48 0.5 MAC and the remifentanyl titrated against patient response (7). This acute tolerance has also been
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50 seen with fentanyl (8, 17).
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55 As stated above tolerance may be expected to differ according to the specific actions of differing opioid
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57 molecules that bind to receptors. For example, methadone acts not only at the μ -opioid receptor but
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59 also the δ -opioid receptor, thus activating supplemental spinal antinocioceptive pathways, and the
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NMDA receptor where it inhibits pronocioceptive activity (18). The use of NMDA receptor antagonists

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3 used as adjuncts to opioid anesthesia to avoid acute tolerance has proved effective in rats (17) but
4
5 ineffective in children (19). In this latter study it was given only per-operatively but some authors claim
6
7 that pre-emptive NMDA co-administration should include the surgery and the postoperative phase to
8
9 be effective (17, 20). Further studies are needed in this regard.

10
11 A curious and apparently paradoxical finding was that administration of 'ultra-low' doses of opioid
12
13 antagonists such as naloxone appeared to enhance the analgesic effects of opioids and to attenuate
14
15 opioid tolerance and liability to dependence. This is thought to be due to switching off release of
16
17 antalgic G_s transmitter proteins which appears to occur at lower dosages that required to switch off
18
19 release of the proanalgesic transmitters G_o and G_i (5).

20 21 22 23 24 25 **Neonatal Neural Development, Tolerance and Addiction (including 'Abstinence')**

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27
28
29 The role of the parent directly affects neonatal addiction where this concerns substances ingested by
30
31 mothers during pregnancy. Additionally, neonates present a different range of considerations due to the
32
33 evolving architecture of their neural architecture and physiology, particularly as fetuses and preterm
34
35 infants. Much has been written recently on the apparent neurotoxic effects of opioids, benzodiazepines,
36
37 ketamine and nitrous oxide on neural integrity (21). Neuronal apoptosis has been observed in animal
38
39 models in response to both infusions and single doses of benzodiazepines. Neural development, such as
40
41 reductions in brain volume, neuronal density and dendritic growth are affected by intrauterine exposure
42
43 to morphine (21). A multitude of agents have been implicated in the appearance of postpartum
44
45 withdrawal phenomena in neonates exposed to substances *in utero*, including chronic ingestion of
46
47 opioids (22-26), benzodiazepines, selective serotonin reuptake inhibitors (SSRIs) (27) and volatile
48
49 substance abuse (28). This 'neonatal abstinence syndrome' is associated with post partum behavioural
50
51 differences in babies (29) and, with some agents, intrauterine growth retardation. Long lasting physical
52
53 stigmata are seen in the 'fetal alcohol syndrome'.

54
55
56 However it must not be assumed that such animal model data extrapolates to human neonates. A very
57
58 recent comprehensive review called into question the applicability of animal models in this regard (21).

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60 The lack of certainty concerning the gestational stage of rodent brain development that reliably

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2
3 matches human brain development was noted. Also, doses of drugs and plasma levels needed to
4
5 produce anesthesia in rodent can be 10-12 times higher than in humans. They also found data that
6
7 document apoptotic activity of ketamine and midazolam in early gestational stages of the rodent fetus.
8
9 However, if these same agents were administered shortly before term, brain development paradoxically
10
11 appears to be enhanced. In the clinical context, a long term multi-centre study from France that
12
13 included a 5-year neurological follow up of very preterm infants showed no difference between those
14
15 receiving sedation and those not (30). Whether short-term anaesthesia is harmful to the human
16
17 neonates brain is still conjectural and is addressed elsewhere in this issue.
18

19
20
21 Neonatal abstinence may be made worse by concurrent brain hypoxia which is also associated with
22
23 increased NMDA pathway activation (31). With such infants presenting for surgery, it is important to
24
25 know to what extent abstinence may affect the anesthetic technique. Unfortunately this does not appear
26
27 to have been studied and reported. It might logically be expected that if the infant is withdrawing from
28
29 opioids, more than usual of this class of drug may have to be employed perioperatively. However, data
30
31 from neonatology suggests that other classes of agents such as chlorpromazine when directly compared
32
33 to morphine as treatment to withdrawing neonates may be as effective in masking opioid withdrawal
34
35 and even shorten the period of treatment of abstinence symptoms (32).

36
37 Other strategies have been tried with the use of partial opioid agonists in the treatment of neonatal
38
39 abstinence. Buprenorphine has been used as a substitute for opium using the Finnegan withdrawal scale
40
41 as monitoring. There were no adverse effects and there seemed to be a tendency to both shorter
42
43 treatment and length of stay but these did not reach statistical significance (25).

44
45 Of relevance to this perhaps, when buprenorphine was compared to methadone in opioid abusing
46
47 mothers, there was more illicit use of opioids detected in the buprenorphine group, suggesting that
48
49 partial agonists were less effective in reducing opioid demand in these mothers (33).
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51 52 53 54 **Tolerance associated with Intensive Care**

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58 Tolerance occurs commonly during sedation in ventilated patients. In a UK-wide study this was seen in
59
60 13% of patients (1) and this has been mirrored in other reports (15, 34). The use of midazolam is

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2
3 particularly associated with the occurrence of withdrawal (1) and a rate of 35% in a PICU population
4 has been reported (3). Overall, withdrawal is associated with duration of sedation and the total doses of
5 agents used (1, 3, 34). In this respect the role of clinicians, nurses and intensivists, must not be
6 underestimated. Where sedation is more tightly controlled by using objective scoring scales (35) it may
7 be possible to minimise excessive use of sedation agents which has been shown to be associated with
8 the subsequent appearance of withdrawal symptoms (1-3, 12, 15, 34). The adoption of such scoring
9 systems has been recommended by a consensus exercise (36). However, there is also emerging
10 evidence of tolerance seen within 72 hours of sedation starting and consequently can occur with
11 relatively short stays on the ICU (1, 15). Withdrawal symptoms in PICU patients may be seen after
12 cessation of sedation within 6 hours in a third of children and in 98% by 24 hours (1).

13 Assessment of withdrawal symptomatology and severity has, for some years, followed that described
14 in neonates by Finnegan. However, recent studies in PICU have described two purpose-built and
15 validated scoring systems for children; the Withdrawal Assessment Tool -1 (WAT-1) (37) and the
16 Sophia Observation Withdrawal Symptoms Scale (SOS) (38). Both these scoring systems now provide
17 an opportunity to record withdrawal phenomena both in terms of frequency and severity in a structured
18 and reproducible manner. This represents an important advance in the study of this common problem.

19 Tapering of sedation and analgesia is often used to try to minimise withdrawal but this takes no
20 account of the pharmacokinetics of many of these drugs which are subject to longish half-lives (2-3
21 hours in the case of morphine and midazolam). This is also made more complex by context-sensitive
22 half-lives, particularly in highly lipid soluble drugs such as fentanyl. Morphine and midazolam have
23 active metabolites, morphine-6-gluconuride and 1-hydroxy midazolam both of which are excreted via
24 the kidney which is often a problem in the ICU. Again, this only serves to compound the problem and
25 muddy the waters with 'tapering'.

26 The effects of disturbed physiology on drug clearance should be anticipated in the critically ill, but in
27 neonates and particularly preterm babies the clearance of many sedative drugs is also prolonged by
28 immature physiology, often markedly. Morphine clearance may only be about 30% of that seen in
29 children over one year of age when adult rates are usually attained (39). This study also showed that
30 clearance is decreased in preterm babies and varies with Post Menstrual Age (PMA) in a non-linear
31 fashion. It also showed that in those born preterm, clearance remained at a lower level when compared
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3 to the same PMA of term babies, at least for the time window of this study; i.e. there was no
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5 acceleration in maturation of clearance occurring as a result of birth.
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7 Metabolites of morphine are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) both
8
9 of which are mostly renally excreted. Although M3G is the predominant metabolite and is
10
11 pharmacologically inert in terms of both analgesia and respiratory depression, about 15% of morphine
12
13 is metabolised to M6G which has analgesia and respiratory depression effects of the same order as
14
15 morphine itself. Formation of these metabolites and their elimination via the kidney are dependent on
16
17 maturation of both the liver and the kidney respectively (40) and where this is probably best described
18
19 in terms of post menstrual age rather than post-natal age (41, 42).
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21 As in neonatal practice, attempts have been made either to forestall withdrawal or treat it with other
22
23 classes of drugs. Recently the use of α_2 -agonist drugs such as dexmedetomidine or clonidine have been
24
25 used in PICUs. Apart from one small prospective study (43), these drugs have been introduced into
26
27 practice in an uncontrolled fashion and a multicentre trial is currently underway in PICUs in the UK
28
29 comparing the use of either clonidine or midazolam for intravenous sedation in a combination with
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31 morphine. These α_2 -agonist drugs have been used to wean patients off 'conventional' sedation with
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33 opioids and benzodiazepines but are now being reported to be associated with withdrawal symptoms
34
35 themselves (13, 14).
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37 Clonidine is being used more frequently to treat or preempt withdrawal symptoms (1), but the
38
39 pharmacokinetics of this drug also vary with age, where neonates demonstrate only approximately 30%
40
41 of the clearance seen in older children (44).
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43 Once withdrawal is identified or anticipated, a practical strategy to deal with this needs to be adopted.
44
45 Now that we have validated withdrawal scoring systems for the paediatric population such as the
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47 Withdrawal Assessment Tool -1 (WAT-1) (37) and the Sophia Observation Withdrawal Symptoms
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49 Scale (SOS) (38), the presence of withdrawal clinical features can be detected and tracked more
50
51 reliably and reproducibly.
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53 In the past it has been usual to taper sedation to allow a gradual re-setting of receptors and enzyme
54
55 systems with a view to preventing decompensatory withdrawal phenomena appearing. Some of these
56
57 tapering schedules may last 1-2 weeks (37) or up to as much as 5-6 weeks using subcutaneous
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59 infusions (45) or oral substitute medications, eg methadone (12). However, evidence on the length of
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time needed to taper varies. A randomised study in a PICU population, utilising methadone to wean

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3 from opioids, found no differences between the group weaned over 5 days compared to the group
4 weaned over 10 days (46) .

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7 Additionally, in a study on withdrawal scoring that used a 'tapering' regimen, symptoms took a median
8 of three days to develop (47), whereas in the UK-wide sedation survey, where sedation was stopped in
9 an uncontrolled manner, these symptoms appeared much sooner (1). There may be something to be
10 said for abrupt cessation of these drugs and dealing with withdrawal symptoms either pre-emptively or
11 swiftly once they occur, rather than delaying what may be inevitable anyway and subjecting these
12 children to prolonged weaning protocols that may not be necessary. Now that reliable systems of
13 withdrawal scoring exist, such a proposal could be tested more reliably.
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27 **Addiction in Clinicians**

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30 It is not just the patients that are vulnerable to agents used in anesthesia or intensive care. A recent
31 survey in the United States showed that of the academic anesthesiology departments contacted, 18%
32 had recorded one or more incidents of propofol abuse or 'diversion' (48). Of the individuals that had
33 been identified, 28% had died as a result of the propofol abuse. Propofol causes tolerance (11) and has
34 psychotropic properties that lend themselves to abuse (49) and this has been corroborated in human
35 volunteers (50). Clearly, anesthesiologists and their immediate co-workers have greater access to such
36 drugs than other physicians and this results in greater drug abuse in this group (51). However, what
37 may be less well appreciated is that in a study utilising mass spectrometry in operating room
38 environments, aerosolized fentanyl was been detected in the air of an operating room, in patients'
39 expiratory circuits and in the headspace above sharps boxes. Aerosolized propofol was also detected in
40 the expirations of a patient undergoing transurethral prostatectomy (52). Given the potential of these
41 drugs to exert effects at minute nanomolar concentrations (53), it may be that occupational exposure is
42 a real hazard for addiction developing in operating room staff. **There needs to be institutional**
43 **recognition of several aspects to this. Tracking of drugs with known addictive potential should be**
44 **rigorous and such drugs should have safe and irreversible disposal. This should now probably include**
45 **propofol and other drugs will undoubtedly emerge that have addictive properties. Lastly, the inherent**
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3 vulnerability of anesthetic and intensive care staff to developing addiction is not solely due to their
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5 obvious access to these drugs but may also be due to subliminal as well as overt occupational
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7 environmental exposure.
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For Peer Review

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