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Norepinephrine dosing in France: Time to move forward!

Isabelle Goyer ¹, Ines Lakbar ², Yonathan Freund ³, Bruno Lévy ⁴, Marc Leone ⁵

¹ Department of Pharmacy, CHU de Caen, Caen, France.

² Anesthesiology and Intensive Care, Anesthesia and Critical Care Department B, Saint Eloi Teaching Hospital, PhyMedExp, University of Montpellier, INSERM U1046, 1, Montpellier, France.

³ Sorbonne Université, IMProving Emergency Care FHU, Paris, France, and Emergency Department and Service Mobile d'Urgence et de Réanimation (SMUR), Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France.

⁴ Service de Réanimation Médicale Brabois, CHRU Nancy, Pôle Cardio-Médico-Chirurgical, Vandoeuvre-les-Nancy, INSERM U1116, Faculté de Médecine, Vandoeuvre-les-Nancy, and Université de Lorraine, Nancy, France.

⁵ Department of Anesthesiology and Intensive Care Medicine, Nord Hospital, Assistance Publique Hôpitaux Universitaires de Marseille, Aix Marseille University, Marseille, France. Electronic address: marc.leone@ap-hm.fr.

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Abstract

Norepinephrine is the first-line vasopressor used in acute cardio-circulatory failure. At the bedside, its dose is critical as it serves to determine the severity of patients, to compare the patients between different studies, and to start specific interventions. Recently, several investigators underlined differences in the expression of norepinephrine doses according to countries and manufacturers. For various reasons, all norepinephrine products are processed to a salt formulation thereby generating a stable and soluble conjugated acid in a slightly acidic solution. Depending on the salt used, the total weight will differ, but the weight of pure norepinephrine base is the same. This results in at-risk situations with large variations in terms of practices, evaluation and treatment. In this technical note, we summarized the evidence and provided a few suggestions to improve the practices at different levels.

Introduction

Norepinephrine (or noradrenaline) is an endogenous catecholamine that is released in case of stress from adrenal glands. It acts on alpha-adrenoreceptors, inducing a contraction of the vascular smooth muscle cell via a calcium-dependent myosin light chain phosphorylation. As a result, the formation of cross-bridges between actin and myosin represents the main mechanism of vascular smooth muscle cell contraction. Norepinephrine additionally activates beta-adrenoreceptors, leading to the production of cyclic adenosine monophosphate (cAMP) and subsequent activation the cAMP-dependent protein kinase [1]. Thus, norepinephrine release is associated with vasoconstriction and an increase in cardiac output. Due to these properties, norepinephrine is widely used in intensive care units (ICU), emergency departments and operating rooms.

The place of norepinephrine in acute care

Norepinephrine is, as of today, the cornerstone of the management of patients with shock. The definition of septic shock relies on the use of a vasopressor, and according to current international guidelines [2], norepinephrine should be used as a first-line vasopressor. Norepinephrine is also recommended for other types of shock, like haemorrhagic shock, and cardiogenic shock [3, 4]. There is also a growing use of norepinephrine in the operating room where its infusion at low concentration tends to become the standard of care to achieve a predefined goal of arterial pressure [5].

The Surviving Sepsis Campaign guidelines suggest introducing vasopressin at pre-determined threshold doses of norepinephrine (0.25 to 0.5 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$ of norepinephrine, corresponding to either the same dose of norepinephrine base or 0.5 to 1 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$ of norepinephrine tartrate) instead of increasing the doses of norepinephrine [2]. Total vasopressor load most often representing norepinephrine dose, is used in daily critical care practice and in clinical research to estimate the severity of illness, predict prognosis or determine the refractory nature of shock.

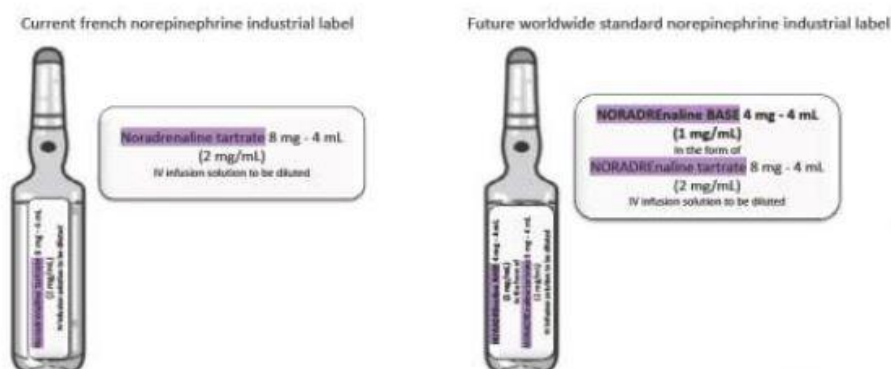
The definition of the sequential organ failure assessment (SOFA) score is based on the dose of norepinephrine or its equivalent, with patient severity escalating in correlation with increased doses of the norepinephrine equivalent [6]. Vasopressor equivalent dose scores such as the Vasoactive-Inotropic Score or the total vasopressor load in norepinephrine equivalents are also based on a calculation referring to the dosage of norepinephrine [7, 8]. Inclusion of patients in several international randomized controlled trials depends on the dose of norepinephrine. For instance, in the ATHOS-3 trial comparing angiotensin-II and placebo in patients with vasodilatory shock, the interventional agent was introduced at a norepinephrine dose of 0.2 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$ [9]. In the operating room, low concentration norepinephrine is widely used via peripheral line based on the results of a randomised controlled trial [5]. However, the discussion around the dilution of norepinephrine is confused by the issue related to the type of norepinephrine [10]. Thus, the dose of norepinephrine is a critical threshold in our daily practice, and, directly or indirectly, dictates a large number of our decisions at the bedside.

The question of norepinephrine dose reporting

Few investigators found some discrepancies among the results of different studies and reported their doubts regarding norepinephrine dose reporting in critical care journals [11-13]. Indeed, the reported doses of norepinephrine differ according to locally available norepinephrine pharmaceutical formulations. Norepinephrine medicinal products are available on the market in the form of injectable aqueous solutions of variable concentrations. To ensure molecular stability and solubility, as well as practicality and safety of intravenous administration, all norepinephrine products must be processed to a salt formulation thereby generating a stable and soluble conjugated acid in a slightly acidic solution. Pure norepinephrine base is unavailable in itself.

At least three different norepinephrine-conjugated salts are available worldwide (tartrate, bitartrate and hydrochloride). Until recently, there was no international standard in terms of industrial product labelling and dose reporting for norepinephrine [14]. Some countries where clinicians predominantly use bitartrate or hydrochloride forms of norepinephrine, such as the United States, have product labels for norepinephrine that first report the content in terms of norepinephrine base equivalency, followed by the total content of the conjugated salt. Conversely, in other countries such as France, where only norepinephrine tartrate is available, the industrial labels most commonly only state product content in terms of norepinephrine conjugated salt. The equivalency in norepinephrine base most often is not clearly disclosed (Fig. 1). As such, norepinephrine doses and concentrations are usually reported in terms of norepinephrine tartrate in France whereas it is most commonly reported in terms of norepinephrine base in North America.

Figure 1 Differences in doses according to norepinephrine labelling (base versus tartrate)



The conjugated salt of norepinephrine is heavier than pure molecular norepinephrine. Depending on the salt used, the total weight will differ, but the weight of pure norepinephrine base is the same. To simplistically illustrate this, another example of a medicinal compound would be sodium. Pure molecular sodium (Na^+) solution is unavailable as a medicinal product. It must be solubilized as a salt (sodium chloride, lactate, acetate, etc). The total weight of the conjugated salt is heavier than pure Na^+ , but pure Na^+ always weighs the same (22.99 mg.mmol⁻¹), no matter the salt used (Table 1).

Table 1

Drug formulation	Total conjugated salt dosing (mg)	Base molecule equivalency (mg)
Norepinephrine tartrate	2	1
Norepinephrine bitartrate	1.89	1
Norepinephrine hydrochloride	1.22	1
Sodium chloride (NaCl 0.9%)	0.9 g (900 mg) / 100 ml	354 mg Na ⁺ + 546 mg Cl ⁻

Investigators also found that major publications often do not clearly state how norepinephrine dosing are reported [11-13]. This situation leaves room for serious misinterpretation depending on the reader's country of residence [14-16]. All in one, discrepancies ranging from single to double were reported in different studies, undermining the reliability of guidelines and clinical practices based on these studies.

Sharing the same language

To meet this challenge, the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) designated an international task force which was in charge of producing a position paper highlighting this issue and suggesting solutions [17]. The task force identified five levels of implication of using different norepinephrine formulations when giving and reporting doses in critical care: 1. Patient safety; 2. Research; 3. Guidelines; 4. Prognostication; and 5. Clinical practice. Six recommendations have been proposed, first, the need to adopt a norepinephrine base as the uniform standard for reporting norepinephrine dosing in ICUs, second, the need for a worldwide uniform norepinephrine dose reporting, third, the need for researchers to clearly state norepinephrine formulation and convert to norepinephrine base in publications, and lastly, the urgent need to homogenize industrial norepinephrine product labelling and reporting to ensure patient safety. In brief, the task force underlined the need for all stakeholders at all different levels (medical teams at the bedside, institutions, national incentives) to speak the same language in terms of norepinephrine dose reporting.

As the norepinephrine formulation used in France diverges from those used abroad and given that France represents a minority in the global context, and to ensure clarity in communication by referring to the "pure" dose, it is logical for us to adjust our practices by transitioning from tartrate to base units for norepinephrine. Therefore, our clinicians, researchers, healthcare workers and agencies should be aware of this issue and we believe that it is our responsibility to attempt homogenization of the use of norepinephrine. All steps of norepinephrine use, all acute care stakeholders (nurses, physicians, pharmacists) and all acute care medical subspecialties are impacted by the homogenization towards reporting of norepinephrine doses in norepinephrine base drug instead of conjugated salt:

- National/international medication safety agencies requirements and marketing authorization (for example European Medicines Agency, *Haute Autorité de Santé*, *Agence Nationale de Sécurité du Médicament et des Produits de Santé*)

- Industrial product marketing and labelling

- Product referencing on the hospital drug formulary
- Medical prescription- Local compounding (dilution)
- Preparation labelling
- Administration
- Reporting/charting in medical record
- Clinical evaluation of patients (based on the dose of norepinephrine they are receiving and calculation of severity and prognostic scores)

Concretely, in day-to-day clinical practice, this implementation of norepinephrine dosing change will mean that all dosing and preparation instructions will be divided into two (Table:2).

Table 2: Examples of how the implementation of norepinephrine base dosing reporting will impact acute care practice

Medication process	Before implementation <i>(current state in France)</i>	After implementation
	Dosing in NE tartrate	Dosing in NE Base
Hospital formulary referencing	Usual institution medication referencing process	Preferentially chose a product which clearly discloses content in NE base on label If not available, hospital pharmacist should perform overlabelling of NE vials
Industrial label	Content in norepinephrine tartrate only	Industrials should be forced by national medication safety agencies to change label Hospital pharmacist should perform over-labelling of NE vials
Nurse/pharmacy compounding	Examples of standard concentrations: 4 mg / 250 ml (16 µg/mL) 2 mg / 50 ml (40 µg/mL) 24 mg / 50 ml (480 µg/mL) Rule of 6 for preparation: 6*weight: final concentration (0.1 µg/kg/min = 1 mL/h)	Favor implementation of standard concentrations: 2 mg / 250 ml (8 µg/mL) 1 mg / 50 ml (20 µg/mL) 12 mg / 50 ml (240 µg/mL) Rule of 3 for preparation: 3*weight: final concentration (0.05 µg/kg/min = 1 mL/h)
Reporting/charting in medical record	Dosing reported in infusion rate Dosing reported in µg/kg/min or mg/h: 0.3 µg/kg/min 1 µg/kg/min 2 µg/kg/min	Favor dosing reporting in dose unit Same units µg/kg/min or mg/h but doses will be halved: 0.15 µg/kg/min 0.5 µg/kg/min 1 µg/kg/min

NE: norepinephrine

The implementation of such a change in norepinephrine dose reporting is a high-risk procedure since it carries a significant risk of medical error during implementation. The potential consequences of an error during prescription, dosing, dilution, administration or documentation of norepinephrine are severe. The fact that clinicians do not know what norepinephrine formulation they use and how they currently report norepinephrine dosing is worrisome and complicates the implementation of this change [18].

In France, representatives of acute care at the National Drug Agency level have been informed about this point and should diffuse the message to the Agency. Multidisciplinary coordination, seamless communication and a step-by-step approach with risk mapping may minimize the patient risk through the implementation process (Fig. 2). A standardized approach to norepinephrine use, for example, use of standard concentrations, standard dosing units, smart infusion systems and automated medical record charting through interoperability can facilitate and secure the change in dose reporting. Such a drastic and ubiquitous change cannot happen overnight at a national level. Norepinephrine users will have to be educated and familiar with the different norepinephrine reporting methods so that they can handle the switch from conjugated salt to base when necessary.

Figure 2 Step-by-step implementation of the Position Statement on norepinephrine dose reporting



Clinicians will also have to learn to interpret newly calculated clinical severity and prognostic scoring tools as well as clinical trial results or recommendations in the light of norepinephrine base dose reporting. For example, the impact on the SOFA score is interesting. The discrepancy in norepinephrine dose reporting induced consistently higher SOFA scores in French patients versus North American patients. When comparing critically ill patient cohorts from France and North America, one could erroneously think that French patients are systematically more severe than North American patients. With uniformization of norepinephrine doses reporting in base, French patients will see their calculated mortality risk significantly decrease (Table 2). Since the SOFA score was initially developed in Europe, probably based on norepinephrine conjugated salt dosing units and then applied worldwide with various norepinephrine dosing units, prospective international studies will be needed to address this uniformization in calculation and its impact on SOFA score prediction of patient mortality [6].

Conclusion

Worldwide uniformization of norepinephrine dose reporting in norepinephrine base is mandatory. A position paper recently suggested expressing norepinephrine doses in base instead of tartrate, harmonizing the protocols in clinical research and alerting manufacturers and agencies to homogenize the practices. In a time where international collaboration for better patient care is needed, we all need to speak the same language facilitated by the adoption of international standard units. This will secure data sharing and pooling for international multicentre studies, facilitate adequate clinical recommendation interpretation worldwide, and ultimately contribute to the elaboration of universal definitions or dosing thresholds for each recommendation on the use of vasopressors.

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