RATE OF FORMATION OF NORPETHIDINE FROM PETHIDINE

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SUMMARY

The concentrations of norpethidine in blood were determined in patients recovering from abdominal surgery following both multiple i.m. injections (i.m. group) and the i.v. infusion (i.v. group) of pethidine. The rate of administration of pethidine averaged 25 mg h\(^{-1}\) in both groups. Concentrations of norpethidine were generally small compared with those of pethidine although the ratio of norpethidine to pethidine concentrations increased steadily over the 2 days studied. The rate of increase of blood concentration of norpethidine was 0.013 \(\mu\)g ml\(^{-1}\) h\(^{-1}\) in both groups of patients. No significant toxic effects were observed.

Norpethidine, a major metabolite of pethidine in man, is produced by the N-demethylation of pethidine and excreted in the urine (Mather and Meffin, 1978). Studies in animals have suggested that norpethidine has both analgesic activity and toxic effects, being reported to have approximately half the analgesic activity and twice the toxicity of pethidine (Schaumann, 1940; Miller and Anderson, 1954; Dahlström et al., 1979). Detection of norpethidine in the blood of animals and man after a single dose of pethidine, administered by a variety of routes, has been surprisingly inconsistent and, although inconsistencies in some studies can be explained by differences in the analytical methods, discrepancies have still been reported using contemporary gas chromatography (Klotz et al., 1974; Szeto and Inturrisi, 1976; Kuhnert et al., 1979).

Blood concentrations of norpethidine associated with analgesia or toxicity have not been determined in the absence of pethidine and its effects in man remain conjectural. Nevertheless, adverse effects after the administration of pethidine in man (Miller and Jick, 1978) may be attributable, at least in part, to norpethidine, especially in patients in whom there is a decrease in the elimination of norpethidine as a result of renal failure (Szeto et al., 1977) or an increase in the formation of norpethidine because of enzyme induction (Stambaugh, Wainer and Schwartz, 1978). This study determined the rate of formation of norpethidine after multiple i.m. injections and the i.v. infusion of pethidine over 2 days following surgery and defined those norpethidine concentrations in the blood which were not associated with overt toxic sequelae.

METHODS

Blood concentrations of norpethidine were determined retrospectively from calibrated gas chromatograms obtained during studies of the analgesic response to pethidine in patients after surgery. Details of the patients and the design of the investigation were described in the original reports (Stapleton, Austin and Mather, 1979; Austin, Stapleton and Mather, 1980a). Briefly, following abdominal hysterectomy, patients were studied for 32 h and received either pethidine 100 mg 4-hourly by injection into the buttock (i.m. group) or a continuous i.v. infusion of pethidine at an average rate of 25 mg h\(^{-1}\) (i.v. group). Complete data were available for six patients of the i.m. group and seven patients of the i.v. group. Norpethidine was detected but not quantitated in the blood of the remaining patients reported in those series. Norpethidine concentrations were determined using the gas chromatographic method of Mather and Tucker (1974) using lignocaine as internal standard and a nitrogen selective detector.

RESULTS

Multiple i.m. administrations

Norpethidine 0.016 \(\mu\)g ml\(^{-1}\) was measured in
the blood of one patient as early as 60 min after the initial i.m. injection. Concentrations increased steadily over the first 4 h and by the end of 8 h after the first injection (that is 4 h after the second injection) the mean (± SD) norpethidine blood concentration was 0.13 ± 0.05 µg ml⁻¹ (n = 6).

Overnight, patients received up to three further injections (administered as required) and by 24 h after the initial injection the mean norpethidine concentration was 0.27 ± 0.09 µg ml⁻¹. At the end of the second day (32 h after operation) the mean concentration of norpethidine was 0.37 ± 0.17 µg ml⁻¹ and was still increasing. The rate of increase of norpethidine concentration was approximately linear, with a rate of 0.013 µg ml⁻¹ h⁻¹ (fig. 1). The ratio of the blood concentrations of pethidine to those of norpethidine varied markedly, because of the fluctuating concentrations of pethidine when compared with the slowly increasing concentrations of norpethidine. The maximum blood concentration of norpethidine measured in any individual was 1.13 µg ml⁻¹.

Continuous i.v. infusion

Norpethidine was detected 40 min after the start of the infusion. Mean concentrations after 8, 24 and 32 h were similar to those from i.m. injections. Again, the rate of increase of norpethidine concentrations was approximately linear, being 0.013 µg ml⁻¹ h⁻¹ (n = 7) and equal to that found in the i.m. group. After 32 h of infusion the blood concentrations of norpethidine had not reached a steady state, despite stable blood concentrations of pethidine (fig. 2).

Adverse effects

Apart from occasional nausea and vomiting, no adverse effects were recorded for any patient which could be associated directly with the pethidine or norpethidine concentrations reported here. None of the toxic effects of norpethidine reported in high-dose animal studies (convulsions, twitching, severe restlessness or respiratory depression) were evident in any patient at any time over the 32 h of the study.

DISCUSSION

Although it has not been determined specifically from direct injection, available evidence (Dahlström et al., 1979) suggests that the elimination rate of norpethidine is slower than that of pethidine. This is supported by our observation that in the i.v. group norpethidine concentrations were continuing to increase after the pethidine concentrations had reached a steady state. Since the absorption of pethidine into the blood after i.m. injection is variable (Austin, Stapleton and Mather, 1980a) it is not surprising to find disparate results for norpethidine after single administrations of pethidine. Such variability tends to become less significant after multiple doses and after an i.v. infusion.

However, adverse effects in man attributable
directly to norpethidine continue to remain unfounded speculation although instances have been reported based on circumstantial evidence (Szeto et al., 1977). For example, one patient with an osteosarcoma of the sacrum received 63 doses of pethidine. He convulsed twice and blood taken before the second convulsion had a plasma norpethidine concentration of 0.67 μg ml⁻¹. No further convulsion occurred after withdrawal of pethidine. A female with chronic renal failure who became irritable after 2 weeks of regular injections of pethidine had a plasma norpethidine concentration of 1.8 μg ml⁻¹. Again, adverse effects ceased on withdrawal of pethidine and with no alteration of other drug therapy. Therefore, Szeto and colleagues advised caution in the use of pethidine in patients with renal failure. However, the real cause of these effects remains unclear.

Nausea, a common adverse effect of narcotic (pethidine) treatment, may result from pain itself (Anderson and Krogh, 1976). Thus, not only is norpethidine implicated because it accumulates with long-term administration, but so is pethidine itself and other metabolites. It is interesting to note that two subjects have received doses of norpethidine 230 and 300 mg i.v. without adverse effects being recorded (Burns et al., 1955).

In animal studies the analgesic activity of norpethidine was one-half to two-thirds that of pethidine. During 32 h of pethidine administration in three separate studies the minimum analgesic concentration of pethidine did not change (Stapleton, Austin and Mather, 1979; Austin, Stapleton and Mather, 1980a, b). These results suggest insignificant, if any, analgesic activity of norpethidine in man from the blood concentrations generated from these dosage regimens.

Unfortunately, evidence for the clinical effects of norpethidine in man is both ill-defined and misleading. Although no relationship between blood concentrations of norpethidine in man and either analgesic activity or toxic effects has been established either in the past or in this study, such effects of norpethidine cannot be discounted completely. Further investigations are required before toxic effects of norpethidine can be established definitively for man. These, like definitive pharmacokinetic studies, should be based on direct injection of the metabolite itself and not on circumstances arising from administration of the parent drug.

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REFERENCES
TAUX DE FORMATION DE LA NORPETHIDINE A PARTIR DE LA PETHIDINE

RESUME
Les concentrations de norpethidine dans le sang ont été déterminées sur des malades récupérant d'une intervention chirurgicale à l'abdomen, après de multiples injections intra-musculaires (Groupe i.m.) et la perfusion par voie intraveineuse (Groupe i.v.) de pethidine. Le taux de l'administration de la pethidine a en moyenne été de 25 mg h⁻¹ dans les deux groupes. Les concentrations de norpethidine ont dans l'ensemble été faibles par rapport à celles de pethidine, bien que le rapport des concentrations norpethidine/pethidine ait augmenté régulièrement au cours des deux journées d'études.

Le taux d'augmentation des concentrations de norpethidine dans le sang a été de 0,013 µg ml⁻¹ h⁻¹ dans les deux groupes de malades. On n'a observé aucun effet toxique significatif.

BILDUNGSGESCHWINDIGKEIT VON NORPETHIDIN AUS PETHIDIN

ZUSAMMENFASSUNG
Es wurden die Konzentrationen von Norpethidin im Blut von Patienten bestimmt, die sich gerade von Unterleibs chirurgie erholten, und zwar sowohl nach multiplen intramuskulären Injektionen (i.m. Gruppe) als auch nach intravenöser Infusion von Pethidin (i.v. Gruppe). Die Verabreichungsgeschwindigkeit von Pethidin betrug durchschnittlich 25 mg h⁻¹ bei beiden Gruppen. Die Konzentrationen von Norpethidin waren im allgemeinen gering im Vergleich zu denen von Pethidin, obwohl das Verhältnis von Norpethidin- zu Pethidin-Konzentrationen im Laufe der zwei Tage ständig anstieg. Die Zunahmegeschwindigkeit der Konzentration von Norpethidin war 0,013 µg ml⁻¹ h⁻¹ bei beiden Gruppen. Es wurden keine bedeutende giftige Auswirkungen beobachtet.

REGIMEN DE FORMACION DE LA NORPETIDINA A PARTIR DE LA PETIDINA

SUMARIO
Se determinaron las concentraciones de norpetidina en la sangre de pacientes en fase de recuperación de intervención quirúrgica abdominal, después de múltiples inyecciones intramusculares (grupo i.m.) y de infusiones intravenosas (grupo iv.) de petidina. El régimen de administración de la petidina promedió 25 mg h⁻¹ en ambos grupos. Las concentraciones de norpetidina fueron, por lo general, pequeñas en comparación con las de petidina, aunque la razón de las concentraciones de norpetidina a petidina incrementó uniformemente durante los días en que se efectuó el estudio. El régimen de incremento de la concentración de norpetidina en la sangre fue de 0,013 µg ml⁻¹ h⁻¹ para ambos grupos de pacientes. No se observaron efectos tóxicos significativos.