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Letters to the Editor

Variability of the blood/plasma concentration ratio of pethidine

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Variability in reported values of the blood/plasma concentration ratio (b/p) of pethidine has been a subject of controversy over the last ten years (Moore & Nation 1976; Mather 1976; Mather & Tucker 1976; Wilkinson & Schenker 1976; Jackson 1981; La Rosa et al 1984). This has resulted in a wide range of blood pethidine clearance values in the literature (Mather & Meffin 1978; Edwards et al 1982) for apparently normal subjects. The variability in reported mean b/p values has been attributed to methodological factors such as sample collection procedure, plasma pH and temperature (Edwards et al 1982). Although more recent reports have tended to arrive at similar estimates of mean pethidine b/p—i.e. around unity, some of these studies still show considerable inter-subject variability.

The purpose of this letter is to draw attention to another source of variability which arises from the fact that b/p is the ratio of two randomly distributed variables: such ratios exhibit greater variability than either numerator or denominator alone (Springer 1979). This can be demonstrated by examining the distribution of a ratio of two independent, normal random variables as a function of the variances of the numerator and denominator. The density function of such a ratio is non-normal and skewed to the right, and its derivation is complex (Springer 1979). Although an approximation of the variance of the ratio can be calculated, we computed the distribution of pethidine b/p using Monte Carlo simulation to enable the range of likely experimental values to be established in addition to the variance. A mean value of b/p = 1 was assigned. The coefficients of variation (CV) of b and p were determined by replicate analyses (Mather & Tucker 1976) on a single large pool of blood and were found to be, respectively, 14·6% (n = 49) and 11·6% (n = 20). Using these values, the distribution of b/p had a CV of 19·4% and was skewed moderately to the right (Fig. 1). A single determination had a probability of 0·95 of taking a value in the range 0·67–1·45, whereas 5 replicates had a CV of 8·9% with 95% of mean values in the range 0·86–1·21. Simulations showed that reducing the assay variability (CV = 5% for both b and p) reduced the CV of b/p to 7·2% with 95% of individual values in the range 0·86–1·17 (Fig. 1).

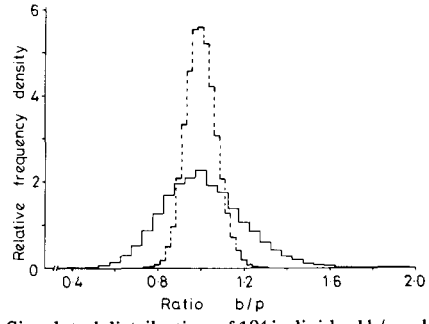

FIG. 1. Simulated distribution of 10^4 individual b/p values by random selection of pairs of b and p from their respective populations. The CVs used were 14·6% for b and 11·6% for p (——) and 5·0% for b and for p (– – – –).

In approximately one quarter of reported studies of pethidine b/p the intra-study CV of b/p was 16% or higher. While factors such as sample collection procedure, plasma pH and temperature may account for bias in mean values of b/p among studies, our simulations show that, in addition, the precision of b and p alone can account for the large variability within studies.

Clearly, a way of avoiding this problem is to use a more precise assay (CV < 5%) and to carry out replicate determinations of b/p in each subject. Both of these approaches were combined by Herman et al (1985) who reported CVs of b/p in young and elderly of 5·9 and 12·4%, respectively. The point we wish to emphasize in this letter is that the approach used by Herman et al (1985) has not been used by most workers. It is apparent that many investigators perform only a single determination of b/p in each subject and convert plasma clearance to blood clearance using this value (Mather & Meffin 1978; Edwards et al 1982). With an assay CV of about 10% our simulations suggest a b/p value of between 0·67–1·45 can be expected. This degree of variability is apparent, for example, in the study of Tamsen et al (1982) in which blood pethidine clearance was calculated from plasma pethidine clearance in each of 10 patients using a single b/p determination for each patient. While the mean b/p ratio was 1·17, individual values ranged from 0·90–1·60.

It is our contention, therefore, that much of the intra-study variability in b/p pethidine ratios is associated with the use of a ratio of two randomly

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distributed variables. Such ratios should be used with caution. Furthermore, the derivation of systemic blood clearance of drugs should be from the measured blood drug for maximum confidence in the value.

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Effect of TRH on acid secretion in the mouse stomach

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Evidence of TRH (thyrotropin-releasing hormone) localization in the entire gastrointestinal tract (Morley 1979) has prompted investigations on the effects of this peptide. Several studies to elucidate the role of TRH in secretory and motility mechanisms have been made (Tonoue et al 1979; Dolva et al 1982; Soldani et al 1983; Oouchi & Ichikawa 1985). However, the results concerning the involvement of TRH in gastric acid secretion are somewhat contradictory, because the type of effect, stimulatory or inhibitory, appears to be related to the route of TRH administration (intravenous versus intracerebroventricular) (Taché et al 1980) and to the secretory stimulus employed (locally or centrally acting). A consistent feature of TRH appears to be its inhibitory effect when gastric acid secretion is elicited by a centrally mediated stimulus, e.g. food, sham feeding, insulin (Gascoigne et al 1980; Konturek et al 1981). As studies on the TRH peripheral effect have all been performed in-vivo, it seemed worthwhile to use a model devoid of extrinsic regulatory influences, therefore we chose the isolated stomach of the mouse, as described by Angus & Black (1978).

Compared with other isolated preparations (oxyntic cells, glands or mucosal sheets), this model has two advantages: preservation of the cellular architecture, necessary for responses to physiological agents, and maintainance of the intrinsic innervation. Therefore the mouse isolated stomach may be considered to be the basic physiological unit for acid secretion (Black & Shankley 1985). This preparation has been widely used in studies on secretion induced by histamine H_2 and cholinergic agents (Angus & Black 1979, 1982; Szelenyi & Postius 1984).

Our results showed that TRH (Relefact TRH, obtained from Hoechst, Italy) in the range of 1–30 μM had no effect on basal gastric acid secretion. However, when secretion was evoked by vagal excitation (electrical stimulation of oesophageal stump at 20 Hz, 10 V, 1 ms, following 15 min incubation with TRH), the peptide induced a significant ($P < 0.05$) inhibition of secretion. This effect of TRH was dose-dependent in the concentration range of 3·2–16·5 μM, the 50% inhibiting concentration of TRH, IC50, being 6·26 μM. TRH affected the secretory peak response, reducing the maximal rate of acid output from 250 to 100 nM H^+ min^{-1}, without interfering with the time of onset (about 10 min). Unlike other antagonists of vagal stimulation, such as atropine and clonidine, which are able to cause a full blockade, the maximal inhibition induced by TRH (9·4 μM) was only about 70%. Neither increasing the concentration of TRH nor adding of the enzymatic inhibitor, phenylmethyl-sulphonylfluoride, could produce a greater antisecretory response. Vagal stimulation of acid secretion is known to depend on release of both acetylcholine and histamine, as it is sensitive to muscarinic (atropine) or H_2 (metiamide) blockers (Angus & Black 1982). TRH may act via a different mechanism, since it was completely ineffective when acid secretion was elicited by the muscarinic agonist bethanechol or by histamine.

It is a matter of speculation at which step of the vagal pathway TRH might interfere. Recent studies show that besides acetylcholine, vagal stimulation induces a release of other neurotransmitters, such as bombesin (Nishi et al 1985), VIP (Larsson et al 1976) and perhaps other peptides. These in turn control gastric acid secretion by releasing other substances, e.g. gastrin, somatostatin (Hirschowitz 1982). TRH might interact with one of these peptides to modify the gastric acid response.

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