LETTERS TO THE EDITOR

Postoperative Sore Throat

Dear Sir,

Like Dr. Cozanitis I too have followed the various communications in your journal concerning the causation of postoperative sore throat.

Many years ago I took an interest in this subject and was surprised to discover in conversation with patients after operation that sore throats were often unilateral or if not unilateral at least worse on the right than on the left. I am sorry that at the distance of some twenty years I cannot produce figures to substantiate this statement, but I can add one observtion which I think is of significance; on some occasions during intubation of a patient I noticed the anterior pillar of the fauces being put under considerable tension during laryngoscopy, which of course a right-handed anaesthetist performs by sweeping the patient's tongue to the left. On one occasion in particular I actually saw this stretched anterior pillar of the fauces break with solution of the continuity of the mucous membrane of the pharynx at this point. These experiences suggested to me that there was a considerable pharyngeal content to postoperative sore throat. A point which is also emphasized by the fact that such discomfort, like that following tonsillectomy can be largely relieved by the administration of aspirin mucilage or even the sucking of a couple of aspirin tablets.

I hope this brief communication will encourage someone who has the facilities to look more fully into this particular aspect of this complication.

Yours faithfully,
Professor A.R. Hunter.
Manchester Royal Infirmary,
Oxford Road, Manchester;
MI3 9WL,
England.

Castor Oil and Drug Absorption

Dear Sir,

We read with great interest, the paper by Gwilt, *et al.*[1]

In the Proceedings of the Annual Meeting of the American Academy of Clinical Toxicologists,[2] we reported an experiment precisely similar to that described by the authors and with exactly similar results.

However, our conclusions differ. We felt that the experiment simply showed that no dialysis of the drug occured back into the gut.

The ligand theory remained to be tested and this was done using coma induced by ethchlorvynol and subsequently treated with supportive care alone, supportive care plus enteric castor oil, supportive care plus mineral oil and supportive care plus phenolphthalein.

A reduction of coma time by 60 per cent was demonstrated in the dogs having either oil added to the treatment regimen. Elimination half lives also showed a significant reduction when either oil was used. No reduction was seen with simple catharsis.[2]

Unfortunately, we were not able to extract as much information from our original data as Gwilt, *et al.* have done. We would not be prepared to state that ethchlorvynol absorption continues for 30 hours in our untreated group or 15 hours in our treated group[3] as they have stated. The authors also go on to suggest using data points after these times to establish Beta slopes. We suggest that two or three data points are inadequate for an acceptable correlation coefficient and any further conclusions based on such a slope would be open to error.

In fairness to the authors, it should be admitted that we were not entirely accurate in our 1976 discussion and only after subsequent experimental work were we convinced of the ligand effect of castor oil and were able to report this in detail in 1980.

In the clinical setting we have not seen an overdose coma caused by lipophillic drugs last over 48 hours in our ICU since the addition of the castor oil routine some ten years ago.

Sincerely,
M.J. Diamond, M.B., F.R.C.P. (C),
R.J. Lee, M.D., F.R.C.P. (C),
M. Keeri-Szanto, M.D., F.R.C.P. (C),
Y.S. Brownstone, M.D.,
Victoria Hospital,
London, Ontario.

REFERENCES

1. GWILT, P.R., PANASKIE, M.C. & MITALA, J.J. The effect of oral castor oil on the disposition of methprylon in intoxicated dogs. Can. Anaesth. Soc. J. *29*: 381 (1982).
2. DIAMOND, M.J., LEE, R.J., KEERI-SZANTO, M. & BROWNSTONE, Y.S. The ligand action of enteric castor oil in the treatment of lipophillic drug overdose. Proceedings of the 1980 Annual Meeting, American Academy of Clinical Toxicologists, Volume 22, Supplement 2, 1980, page 45–47.
3. DIAMOND, M.J., BROWNSTONE, Y.S., ERCEG, G., KIERASZEWICZ, H. & KEERI-SZANTO, M. The reduction of coma time in lipophillic drug overdose using castor oil. Can. Anaes. Soc. J. *23*: 170–175 (1976).

PHARMACOKINETICS OF MEPERIDINE INFUSION

DEAR SIR,

We have read with interest the paper by Sprigge, *et al.*[1] concerning continuous meperidine infusions in morbidly obese patients. In particular, we noted the success of the narcotic infusion in providing analgesia for the patients. However, we were concerned about the pharmacokinetic data reported in this paper.

In contrast to previous investigations with single doses of fentanyl in obese patients,[2] but in overall agreement with meperidine given by continuous infusion in non-obese patients,[3] results reported by Sprigge, *et al.*[1] suggest that increased total body clearance of narcotic occurs with increased body weight. However, it is the *magnitude* of the clearance and its apparent time dependence that has caught our attention.

Using the data presented in Figure 4,[1] we have estimated mean total body clearance (Cl) of meperidine in these morbidly obese patients by two methods. The first employs the following relationship which is an expression of the Fick Principle:

$$Cl = \frac{D}{AUC_{18} + AUC_{18\text{-}\infty}} = \frac{D}{3.3 + 0.9}$$

$$= \frac{800\ mg}{4.2\ mg \cdot hr \cdot l^{-1}} = 3.2\ l \cdot min^{-1}$$

where D is total dose infused intravenously and AUC_{18} and $AUC_{18\text{-}\infty}$ are the areas under the plasma concentration-time curve, respectively, calculated by application of the trapezoidal rule from 0 to 18 hr and extrapolated from 18 hr to infinite time. The calculated value of $AUC_{18\text{-}\infty}$ determined from the available data will be an overestimate because it is based on the extrapolation of the slope of regression of concentrations from 3 to 18 hours on time *while the infusion is continuing*. In fact, cessation of infusion at 24 hr would produce an even faster rate of decrease of plasma concentrations. Hence Cl is underestimated by this calculation.

The second method is also based on the Fick Principle. At steady state:

$$Cl = \frac{Ko}{C_{ss}} = \frac{0.5\ mg \cdot min^{-1}}{0.3\ mg \cdot l^{-1}} = 1.7\ l \cdot min^{-1}$$

where Ko is the zero order infusion rate producing the mean steady state plasma concentration C_{ss}. However, the value used for C_{ss} ($0.3\ mg \cdot l^{-1}$, occurring at 1–3 hours) is not, in fact, an indication of a true steady state. Surprisingly, the mean concentration decreased to $0.21\ mg \cdot l^{-1}$ at 6 hours and $0.08\ mg \cdot l^{-1}$ at 18 hours. Now the time to reach steady state is approximately five multiples of the "terminal" half life of the drug, but this can be foreshortened through loading infusions as carried out by Sprigge, *et al.* If the 18 hour concentrations are taken as C_{ss}, the new value of Cl is equivalent to $6.3\ l \cdot min^{-1}$.

The physiological significance of Cl is that total body clearance is equal to the sum of the products of blood flow to and extraction ratio at each of the organs or tissues capable of irreversibly removing drug. Meperidine is removed from the body primarily by hepatic biotransformation[4,5] so that its total clearance can scarcely exceed hepatic blood flow (corresponding to total hepatic extraction). The conservative estimates of meperidine clearance, calculated above, clearly exceed hepatic blood flow. In fact, they suggest that the clearance may even exceed cardiac output! (Even allowing for differences between equivalent plasma and whole blood concentrations, most estimates of mean meperidine clearance are in the range $0.5–1\ l \cdot min^{-1}$).[4,5]

It should be noted that clearance from the body has to be distinguished from distribution within the body. This is implied in the area under the curve calculation where drug lost to tissue when the blood to tissue concentration gradient is high will be regained when the gradient is reversed. However, the data obtained by Sprigge, *et al.*[1] describing a continuously decreasing plasma concentration suggest a continued tissue (fat?) uptake or a very high and continuously