SYMPTOMATIC BRADYCARDIA IN ASSOCIATION WITH H_2-RECEPTOR ANTAGONISTS

SIR,—Ranitidine is thought to be specific for histamine H_2-receptors. It relieves symptoms of reflux oesophagitis and Zollinger-Ellison syndrome and heals duodenal ulcers. No major side-effects have been reported,[1] although controversy has surrounded its specificity and its effect on heart rate.[2,3]

Camarri et al.[2] reported bradycardia in two patients given ranitidine but the manufacturers ascribed this either to the high intravenous doses of the drug that were used coupled with the effect of blood transfusion or to the patient's advanced age.[3] Jack et al.,[3] in their table I, provide means and SEMs for heart rates in patients before and after taking ranitidine. However, unless the pulse rates were normally distributed, comparison of median rates and a rank significance test might have been more revealing. Their table I suggests that the upper 1% of the 1990 pre-treatment heart rates lay between 109 and 169 beats/min while the upper 1% of the 1766 heart rates during treatment with ranitidine 150 mg twice daily were between 105 and 126 beats/min. I would like to report a case of marked dyspnoea due probably to bradycardia in association with ranitidine.

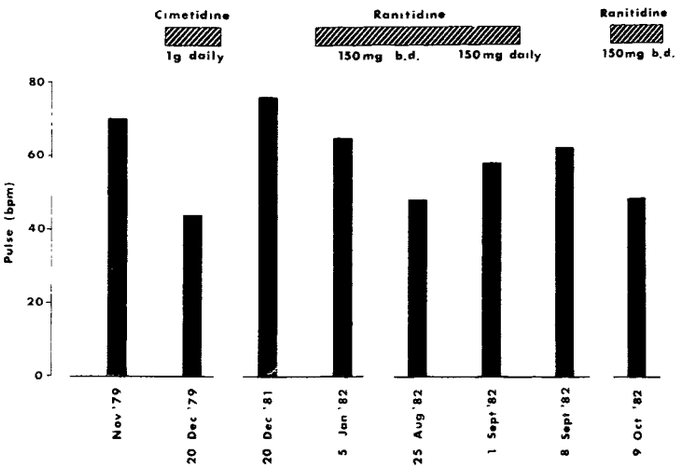
A 71-year-old woman with a history of ischaemic heart disease and hiatus hernia began to experience severe heartburn and epigastric pain. Hiatus hernia with reflux oesophagitis was confirmed. She was normally only a little dyspnoeic on exertion. Her cardiovascular and respiratory status was satisfactory, with a pulse rate of 76 beats/min and a blood pressure of 130/70 mm Hg (which did not change significantly at follow-up examinations). There was no clinical or biochemical evidence of hepatic or renal dysfunction. Ranitidine 150 mg twice daily was added, with considerable symptomatic relief from oesophagitis, to her existing treatment with two tablets daily of 'Navidrex-K' (cyclopenthiazide and potassium). 2 weeks later, she began to feel dizzy and her pulse rate had dropped to 65/min. Atropine 0·6 mg twice daily for 2 weeks failed to raise her pulse rate. A carotid bruit was heard but her symptoms and bradycardia (54–60 beats/min) persisted despite a carotid endarterectomy. No neurological abnormality could be found despite many investigations. She deteriorated over the next few weeks and was dizzy, tired, and markedly dyspnoeic even at rest. On Aug. 25 it was suspected that her dyspnoea and bradycardia (then 48/min) might be related to ranitidine. The drug was stopped in two steps with progressive increase in her pulse rate to 62/min and a marked improvement in her dyspnoea and other symptoms.

Over the next 4 weeks, her symptoms of hiatus hernia recurred and began to trouble her even more severely than before. She was therefore rechallenged with ranitidine 150 mg twice daily, at a time when her pulse was 60/min. Her symptoms of hiatus hernia improved but within 60 h (five doses of 150 mg ranitidine), her dyspnoea had increased markedly and her pulse rate had dropped to 48/min with recurrence of dizziness. Her daily pulse rate ranged between 48 and 55/min and attempts to raise it with sustained-release isoprenaline (30 mg orally daily for a week) failed and ranitidine had to be discontinued. Her dyspnoea, dizziness, and bradycardia (post-ranitidine heart rate on Oct. 27 68/min) resolved once again and surgery was offered for her hiatus hernia.

This patient had been treated with cimetidine (200 mg three times daily with 400 mg at night) 3 years earlier. A few days after starting cimetidine, she had experienced severe dizziness, marked dyspnoea at rest, and lethargy. Her pulse rate had dropped to 44/min. No other cause for this bradycardia could be found. Her symptoms and bradycardia resolved completely within a few days of discontinuing cimetidine.

The effects of H_2-receptor antagonists on the pulse rate of this patient are shown in the figure.

The patient was only on a thiazide diuretic apart from ranitidine and the temporal relationship between ranitidine treatment and the



Effect of H_2-receptor antagonists on pulse rate.
For pulse rates before and after the October, 1982, ranitidine re-challenge see text.

deterioration in her dyspnoea and the onset of bradycardia is strongly suggestive of ranitidine as the cause. It looks as if ranitidine may not be as specific for gastric H_2-receptors as hitherto thought. The drug did not affect atrioventricular conduction, as judged by the PR interval on electrocardiograms (150 ms throughout). Cimetidine also produced symptomatic bradycardia in this patient, lending further support to a role for H_2-receptor antagonism in the aetiology of her bradycardia. Coexisting ischaemic heart disease may predispose to the adverse cardiac effects of H_2-receptor antagonists.

This patient is a poor oxidiser of debrisoquine (metabolic ratio 33·5)[4] and may be especially susceptible to the adverse effect of some drugs.[5] Ranitidine is normally subject to extensive presystemic metabolic elimination[6,7] by oxidation but this has not been studied in poor metabolisers of debrisoquine. In any case the evidence[8,9] is against this particular genetic control over ranitidine metabolism. A role for histamine receptors in the heart cannot yet be excluded.

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WERNICKE'S ENCEPHALOPATHY IN PROLONGED FASTING

SIR,—Wernicke's encephalopathy resulting from thiamine deficiency is a well known complication of alcoholism, stomach cancer, pyloric stenosis, and hyperemesis gravidarum.[1] Intravenous alimentation may also be a cause.[2] We are aware of another category—healthy individuals on prolonged voluntary fasting or hunger strike—and report an illustrative case.

A 32-year-old Baptist pastor embarked on a total fast to enhance his spiritual powers for exorcism. He had been in excellent health and did not drink. During the fast, he took plain tap water only. On the 35th day he vomited once and behaved strangely: he sang hymns wildly and irrationally and his gait was unsteady. On the 42nd day he had three convulsions and was admitted to hospital in a stuporous state.

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3 Jack D, Richards DA, Granata F. Side-effects of ranitidine. *Lancet* 1982, ii. 264–65
4 Price Evans DA, Mahgoub A, Sloan TP, Idle JR, Smith RL. A family and population study of the genetic polymorphism of debrisoquine oxidation in a British white population. *J Med Genet* 1980, **17**: 102–05
5 Smith RL, Idle JR. Genetic polymorphism in drug oxidation. In: Davis M, Tredger JM, Williams R, eds. Drug reactions and the liver. Bath: Pitman Medical, 1981 95–104
6 Bell JA, Dallas FAA, Jenner WN, Martin LE. The metabolism of ranitidine in animals and man. *Biochem Soc Trans* 1980; **8**: 93
7 Weidler DJ, Battodeno N, Eshelman FN. Pharmacokinetics of ranitidine, a new histamine H_2-receptor blocker. *Clin Pharmacol Ther* 1981; **29**: 247–48
8 Kupfer A, Al-Dabbagh SG, Ritchie JC, Idle JR, Smith RL. Spectral binding studies of the polymorphically metabolized drugs debrisoquine, sparteine and phenformin by cytochrome P-450 of normal and hydroxylation deficient rat strains. *Biochem Pharmacol* 1982; **31**: 3193–99
9 Rendic S, Alebic-Kolbah T, Kajfez F. Interaction of ranitidine with liver microsomes. *Xenobiotica* 1982, **12**: 9–17
1. Editorial. Wernicke's encephalopathy: Review article. *Br Med J* 1979; ii: 291–92.
2. Harper CG. Sudden unexpected death and Wernicke's encephalopathy. A complication of prolonged intravenous feeding. *Aust N Z J Med* 1980, **10**: 230–35.

Neurological examination revealed pupils equal and reactive; total loss of oculocephalic reflex horizontally and no response to ice-cold water irrigation of both ears; spontaneous vertical nystagmus; fundi normal; deep tendon reflexes were diminished and plantar response was upgoing bilaterally. No cardiac abnormalities were noted.

Blood glucose was 80 mg/dl; nevertheless 100 g dextrose was administered intravenously in the emergency unit. 8 h later a neurologist felt he should be treated for Wernicke's encephalopathy. 400 mg of thiamine with vitamin B complex was infused intravenously and another 600 mg was given over the next 24 h. A computerised tomographic scan of the head was normal. CSF examination and biochemistry (blood urea and electrolytes) were also normal. EEG showed diffuse, synchronous, bilateral slow waves consistent with a metabolic encephalopathy. Auditory evoked potentials showed delay of interpeak latencies: P_1-P_5 = 4·70 ms (normal <4·54); P_1-P_3 = 1·81 ms (normal <2·64); P_3-P_5 = 2·89 ms (normal <2·84).

The serum pyruvate level (2 h after thiamine administration) was 1·0 mg/dl (normal below 1·2). Transketolase assay could not be done.

Within 24 h of administration of thiamine the patient regained consciousness and could answer simple questions rationally. He could deviate his eyes laterally on command but gaze-dependent nystagmus was still present. Memory for recent events was still deficient. He experienced vertigo when fixating. Nerve conduction of the median, posterior tibial, and sural nerves confirmed a sensorimotor neuropathy. After a week on a normal diet with vitamin supplements, the patient recovered sufficiently to be discharged. 3 months later, he was completely well and there were no residual signs. Repeat brainstem evoked potential, EEG and, nerve conduction studies were normal. For the first month after discharge, he had difficulty recognising the streets in the city, but gradually his memory returned.

The signs on admission suggested Wernicke's encephalopathy and the response to thiamine confirmed the diagnosis. The serum pyruvate was normal but this was after thiamine administration. Stockard found no delay in brainstem-evoked potentials in Wernicke's encephalopathy[3] but our patient had delayed interpeak latencies which improved with treatment. A peripheral neuropathy also developed.

Brin[4] found no clinical deficiency symptoms in patients given an almost thiamine-free isocaloric diet for up to 6 weeks, although Ziporin et al.[5] estimated that by the 18th day of thiamine-free isocaloric diet in normal adults the body is depleted of its stores. In total fasting and physical inactivity this risk might be expected to be reduced.[6] Endogenous fat breaks down, especially in obese subjects, to provide much of the minimal energy requirement by pathways that do not require thiamine. Vitamin B_1 is a co-factor coenzyme in decarboxylation of α-ketoacids that arise from metabolism of glucose derivatives and, to a lesser extent, aminoacids.[7] Drenick[8] casts doubts on this assumption by reporting an obese truck driver with Wernicke's encephalopathy 30 days after a 500 calorie diet without vitamin supplements. Our patient had classical encephalopathy while on total fasting: he was not obese and had been on a normal diet before fasting.

We think that subjects on hunger strike when they lapse into coma or delirium, should be treated with large doses of vitamin B_1 and B complex together with intravenous fluids and other resuscitative measures. Harper noted coma without typical eye signs in his hyperalimentation patients who were thiamine deficient. Moreover, some individuals may have a genetic abnormality in the kinetic properties of transketolase, thus predisposing them to Wernicke's encephalopathy.

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MATERNAL ANALGESIA AND SATISFACTION

SIR,—The report by Dr Morgan and her colleagues (Oct. 9) is unsatisfactory. Of the 1000 mothers only two-thirds replied to the twelve-month follow-up postal questionnaire (itself a notoriously unreliable method of obtaining information about subjective responses). How many women in all of the nine "analgesia groups" responded and to what extent did imbalance between the groups bias the comparisons between experience scores recorded twelve months after the event? On the assumption that the response rate was roughly the same in every group, the data contain some striking information. In all groups dissatisfaction was much more common in retrospect than it had been in the postnatal period. Among women who had received no analgesia or those who had either 'Entonox' alone or pethidine alone, the percentage increases in the "dissatisfaction score" were 250, 287, and 256, respectively. Among those given an epidural only the figure was 186%. The increases among women given an epidural plus pethidine or an epidural plus entonox were 242% and 250%, presumably reflecting the fact that an epidural was given because the other drugs had provided insufficient analgesia.

Morgan et al. contend that mothers who refused all analgesia reported "high indices of satisfaction both immediately and a year later". This begs two questions. Firstly, it is hardly surprising that mothers who were treated in a manner which they requested—a policy which we follow, in common with most major U.K. obstetric units whose policies I am aware of, including, apparently, Queen Charlotte's, where "epidural analgesia was available *to all requesting it*" (my italics)—would express themselves as being satisfied. Secondly, what is a "high index of satisfaction"? Even taking the figures in table I at their face value there is little difference between the groups in respect of experience score, and this would become even less if the 24 women who had a pudendal block only (and thus presumably declined analgesia during labour up to the time of delivery) were to be included in the "no analgesia" category.

I am saddened by the revelation that epidurals seem so poorly effective in the provision of analgesia at Queen Charlotte's. Our experience over the past fourteen years mirrors that reported from all other major units. Certainly we have failures (3–4%) and partial failures (10%), but the extent of failure to achieve adequate analgesia reported by Morgan et al. suggests something seriously wrong with either the antenatal counselling or the conduct of epidural analgesia at Queen Charlotte's. Perhaps the hospital's patients are drawn from too far afield to permit adequate communication throughout pregnancy, labour, and delivery.

Morgan et al. imply that if a labour is rendered painless it will be longer. Several stringently analysed studies have demonstrated that a continuous lumbar epidural block has very little infuence upon the mean duration of the first-stage of labour and that it corrects the tendency to prolongation of the first stage in mothers who are becoming fatigued.

Morgan et al. state that "it seems that the expensive provision of an 'epidural on demand' service is unnecessary". I thought that one of the current campaigns was to favour providing women in labour

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