

SHORT REPORTS

Cardiac arrest after treatment with intravenous domperidone

Domperidone (Motilium, Janssen Pharmaceuticals) is a widely used antiemetic. We report four cases of cardiac arrest after intravenous administration of this drug.

Case reports

Case 1—A 53 year old woman with inoperable ovarian carcinoma was receiving treatment with cisplatin. Before starting treatment she had been clinically well with normal electrolyte concentrations (potassium 3.7 mmol(mEq)/l; normal 3.4-5.0 mmol/l). She was given domperidone 50 mg in one litre physiological saline over two hours just before and after the cisplatin infusion. Treatment on day 1 proceeded uneventfully, but during the second domperidone infusion on day 2 she collapsed with apnoea, dilated and sluggishly reacting pupils, and absent circulation. She was successfully resuscitated. The plasma potassium concentration was 3.2 mmol/l.

Case 2—A 33 year old woman with stage IV non-Hodgkin's lymphoma had fever and tachycardia. Before starting chemotherapy she received domperidone 50 mg in 100 ml physiological saline over 15 minutes. Towards the end of the infusion she developed ventricular fibrillation, from which she was successfully resuscitated. Plasma potassium concentration was 2.9 mmol/l.

Case 3—A 38 year old woman with acute promyelocytic leukaemia was being treated with daunorubicin, cytarabine (cytosine arabinoside), and thioguanine. She had received 530 mg daunorubicin. She was also being treated for septicaemia with intravenous vancomycin, gentamicin, amphotericin, and metronidazole. Five minutes after receiving domperidone 20 mg and cimetidine 400 mg (slow intravenous bolus injections), and during infusion of vancomycin 500 mg (in 100 ml physiological saline over 30 minutes), she collapsed and was found to be pulseless and apnoeic with dilated pupils. She was successfully resuscitated. Plasma potassium concentration was 2.0 mmol/l. The episode was initially attributed to the vancomycin, and she received further intravenous domperidone without adverse effect.

Case 4—A 37 year old woman with acute myeloid leukaemia was being treated with daunorubicin, cytarabine, and thioguanine. She had received 240 mg daunorubicin. Treatment with amikacin and cefotaxime had been stopped 12 hours earlier. She was clinically well with no fever. After receiving a bolus of domperidone 20 mg and during administration of a bolus of cytarabine 160 mg she complained of dizziness and loss of vision. Her pulse was irregularly irregular. An electrocardiogram showed multifocal ventricular extrasystoles and salvos of ventricular tachycardia, which were abolished by lignocaine 100 mg. Plasma potassium concentration was 2.1 mmol/l and she was given a potassium chloride infusion. The arrhythmias were attributed to the cytarabine and hypokalaemia. The next evening she was given a bolus of domperidone 20 mg before chemotherapy and immediately developed multifocal ventricular extrasystoles, which were again treated with lignocaine. Despite this she developed ventricular fibrillation, from which she was resuscitated with a single direct current shock. Plasma potassium concentration was 3.1 mmol/l.

Comment

All four patients suffered cardiac arrest after receiving intravenous domperidone. None had a history of ischaemic heart disease or cardiac arrhythmia, and none had any arrhythmia subsequently.

Domperidone is a relatively new antiemetic drug that is at least as effective as metoclopramide in relieving the nausea and vomiting induced by moderately emetic chemotherapy.^{1,2} Its main advantage over metoclopramide is its freedom from side effects.¹⁻³ Cardiac arrest has been noted previously after an intravenous bolus of 200 mg domperidone,⁴ although the manufacturers disputed the drug's role in precipitating the event.⁵ Six cases of cardiac arrhythmia associated with domperidone have been reported to the Committee on the Safety of Medicines (CSM). Although three of our patients had hypokalaemia at the time of their cardiac arrest, this was appreciable in only one. Hypokalaemia was noted in only two of the cases reported to the Committee on the Safety of Medicines (J C P Weber, personal communication), one of which was our case 2. We and others have found that in the low dose recommended by the manufacturers for patients receiving cytotoxic chemotherapy the antiemetic effect of domperidone is disappointing^{1,2,4}; the drug is commonly used in higher doses because of the absence of side effects.

We conclude that as domperidone may cause potentially fatal cardiac arrhythmias when given in doses adequate to protect against

the emetic effects of cytotoxic chemotherapy its use as an antiemetic for patients receiving such treatment is questionable.

We thank Professor F G J Hayhoe for permission to report cases 3 and 4.

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Prevalence of migraine in patients with diabetes

Migraine is induced in susceptible people by several factors including fasting.¹ This has led to the suggestion that blood glucose concentrations may influence the onset of an attack of migraine. If some relation exists between migraine and blood glucose concentrations the prevalence of migraine might be expected to differ between subjects with and without diabetes. Blau and Pyke studied patients with migraine and diabetes and noted that some patients either lost or showed an appreciable reduction in their migraine attacks with the onset or control of diabetes.²

To assess whether the prevalence of migraine differs between diabetic and non-diabetic people we asked 850 subjects to answer a questionnaire on headaches.

Subjects, methods, and results

A questionnaire based on that reported by Taylor *et al*³ was given to 278 patients with diabetes in Southampton and 263 in Basingstoke. The patients were consecutive attenders at the outpatient diabetic clinics. Severity or duration of the disease was not assessed. The subjects completed the questionnaire themselves, with help from WKB whenever sought. Two hundred and fifty (90%) of patients in Southampton and 250 (95%) in Basingstoke completed the questionnaire.

One hundred and ninety one consecutive attenders at the fracture and general surgery clinics in Southampton and 159 at the fracture and accident and emergency clinics in Basingstoke served as controls (incidence of response 90%). They answered the same questionnaire as the diabetic patients.

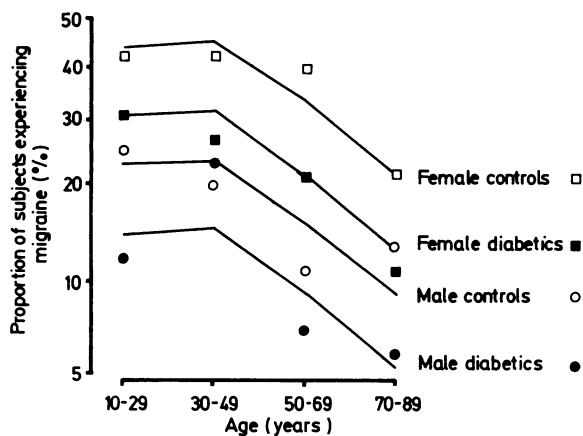
Three of the most distinctive features of migraine are a unilateral distribution of headache, a warning that headache is coming, and nausea accompanying headache. For this study patients who had at least two of these features were considered to have migraine.

For statistical analysis we used logit linear models and examined the influences of sex, age, town, and whether the subject had diabetes, on the prevalence of migraine.

The figure shows the proportions of diabetic and control subjects with migraine by age and sex together with the fitted model that assumes a parallel response on the logit scale to age, sex, and whether diabetic. The most important variable in determining the prevalence of migraine was sex, with 126 (29%) of the women having migraine compared with 411 (15%) of the men ($\chi^2=26.1$, $df=1$, $p<0.001$). The proportion with migraine decreased from 44 out of 164 (27%) in the youngest subjects to 15 out of 126 (12%) in the oldest. The effect of age, adjusted for sex, was significant ($\chi^2=24.4$, $df=3$, $p<0.001$). Prevalence of migraine was similar in subjects from Basingstoke and Southampton (22.5% and 21.6% respectively).

The prevalence of symptoms of migraine was lower in diabetic patients (17%) than controls (29%). The corresponding comparison adjusted for

both age and sex was significant ($\chi^2=10.7$, $df=1$, $p \approx 0.001$). This excess in controls over diabetics of more than three to two was roughly constant at all ages and in both sexes.



Prevalence of migraine in 500 diabetic patients (256 females) and 350 controls (178 females) by sex and age.

Comment

This study showed that, of patients attending outpatient clinics, those with diabetes suffered significantly less from migraine than those without diabetes. The explanation for this finding was not clear but it may have been associated with an underlying anomaly of carbohydrate metabolism that may exist in patients with migraine. Hockaday has suggested that the central response to absolute or relative shortage of carbohydrate supply might be abnormal in some patients with migraine and that this could lead to a neurogenically determined attack.⁴ Further biochemical investigation of patients with both migraine and diabetes may lead to a better understanding of the influence that blood glucose concentrations have on the genesis of a migraine attack.

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Biodegradable polymer luteinising hormone releasing hormone analogue for prostatic cancer: use of a new peptide delivery system

Peptide analogues have recently provided new treatments for various medical conditions ranging from nocturnal enuresis to malignancy.^{1,2} Considerable interest has been shown in the use of luteinising hormone releasing hormone analogues as first line treatment for prostatic cancer. Initial reports showed an excellent clinical and endocrine response.³ Such analogues given by intermittent bolus administration, either subcutaneously or intranasally, however, may stimulate rises of luteinising hormone and in some cases testosterone concentrations in the period after drug administration, even after many months of treatment,⁴ which precludes this type of administration over long periods. The likely mechanism of this intermittent stimulation of luteinising hormone and testosterone release is phasic peaks of peptide

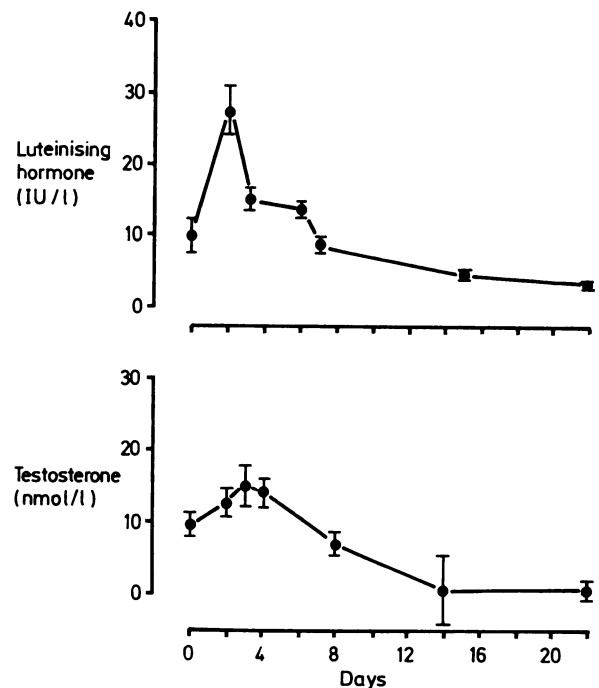
which result from an intermittent bolus administration of these analogues. Possibly a depot formulation in which drug is continuously available would overcome this problem. We report preliminary endocrine studies of a depot preparation of one such analogue, Zoladex (ICI 118630), which is administered subcutaneously every 28 days.

Patients, methods, and results

We studied eight patients with newly diagnosed advanced metastatic prostatic cancer who had not previously received any form of endocrine treatment. The depot preparation, which consists of 3.6 mg of the luteinising hormone releasing hormone analogue bound to a biodegradable lactide and glycolide polymer,⁵ was given by subcutaneous injection into the anterior abdominal wall every 28 days. Endocrine assessment of serum testosterone and luteinising hormone concentrations was performed at intervals throughout the study. A 24 hour profile 15 days after the sixth depot injection was also performed.

Serum luteinising hormone—The mean serum luteinising hormone concentration rose to twice the basal value within two hours of the first depot injection, and continued to rise to a maximum at 48 hours (figure). Down regulation to predose values occurred by day 8, and full suppression by 21 days. Twenty four hour profiles of luteinising hormone studied after the sixth depot injection showed no change in values, which remained fully suppressed throughout the period of study.

Serum testosterone—Seven of the eight patients had a serum testosterone concentration within the normal range at the beginning of the study. In one patient the value was in the castrate range and remained so throughout. In the other seven patients maximum stimulation occurred by day 4, and down regulation to basal values by day 8 (figure). Substrate values of testosterone—that is, less than 3 nmol/l (0.9 ng/ml)—were achieved by day 15 in all patients. Testosterone remained at that value throughout the period of study.



Changes in mean serum testosterone and luteinising hormone concentrations after first depot administration of analogue.

Conversion: SI to traditional units—Testosterone: 1 nmol/l \approx 0.29 ng/ml.

Apart from mild discomfort lasting less than half an hour, no symptoms at the site of injection were reported by any patient. No worsening of symptoms was seen in any patient during the initial gonadotrophin stimulatory phase. At six months no patient showed signs of progression of disease. Three had a greater than 50% reduction in size of the prostate, and acid phosphatase activity returned to normal in those in whom it had been raised.

Comment

The discovery that superactive luteinising hormone releasing hormone analogues lower testosterone values to a greater degree than stilboestrol and that they are at least as effective in the treatment of prostatic cancer has revolutionised care of this condition.