DRUG POINTS

Arthralgias and omeprazole

Ms M Beutler, Ms K Hartmann, Dr M Kuhn, and Professor J Gartmann (Swiss Drug Monitoring Centre, CH-700 Chur, Switzerland) write: We describe five cases of arthralgia associated with omeprazole. In all cases the patients were treated with 20-40 mg omeprazole daily.

A 27 year old woman was given omeprazole for a duodenal ulcer that was unresponsive to ranitidine. After 10 days she developed swelling of her fingers, knees, and ankles, with pruritus and erythema over the metacarpal joints. Treatment was stopped and symptoms disappeared within 10 days.

A 79 year old woman with gastric cancer was given omeprazole for ulcerating gastritis. She was also taking midazolam, antacids, and cisapride. After starting omeprazole she developed intermittent pain and swelling of her joints. The results of laboratory tests for rheumatoid arthritis, systemic lupus erythematosus, and infection were negative. The polyarthritis resolved after stopping the drug.

A 57 year old man was given omeprazole for gastric erosions. Two weeks later he developed polyarthralgia and erythema nodosum of the right lower leg. The symptoms and signs resolved 18 days after withdrawal of omeprazole.

A 50 year old man with oesophagitis developed interphalangeal joint pain three to four months after starting omeprazole. The pain subsided rapidly on withdrawal of the drug. On taking omeprazole two months later he experienced discomfort in the small joints of his hand; this again resolved on stopping the drug.

A 71 year old man was receiving long term treatment with diclofenac, tramadol, methotrexate, and fluoride for polyarthritis. He was also taking oxazepam, digoxin, and ranitidine. Two days after replacing ranitidine with omeprazole because of a relapsing duodenal ulcer he felt an increase in joint pain which improved after stopping the drug. Several rechallenge tests produced the same pattern.

In the first three cases arthralgia developed 10-20 days after starting omeprazole and disappeared after stopping it. The third patient also developed erythema nodosum, a single case of which has previously been reported to the manufacturer. In the fourth case the reaction was delayed, although an underlying rheumatological disease cannot be excluded. The last patient's polyarthritis may have been aggravated by omeprazole either as a direct effect or through a drug interaction.

The Swedish Adverse Drug Reactions Advisory Committee has reported six cases of headache during omeprazole treatment; in some cases headache was accompanied by myalgia or arthralgia.[1]

1 Swedish Adverse Drug Reactions Advisory Committee. Omeprazole—two years on the market. *Bulletin from SADRAC* 1991; No 59:1-3.

Anisocoria associated with selective serotonin reuptake inhibitors

Dr J Barrett (Maudsley Hospital, London SE5 8AZ) writes: Uneven pupillary dilatation was seen in a 28 year old junior doctor who was taking no other drugs and was being treated for a depressive disorder with sertraline. Although he usually had equal pupils, when he took 150 mg sertraline daily both of his pupils became dilated, the left more so by about a quarter. Treatment had started at 150 mg, and the effect had been noticed soon afterwards. It reversed within 48 hours of stopping treatment.

A similar effect was seen in a 33 year old woman seen in the accident and emergency department after an episode of minor self harm. She had been taking paroxetine for four weeks at a dose of 50 mg daily and no other drugs, apart from half a bottle of sherry daily, which she had been taking for some months. She and her sister confirmed that she did not usually have unevenly dilated pupils, and she volunteered that this had occurred since taking paroxetine. Had the uneven dilatation been observed by the casualty officer and been confirmed as abnormal for the patient, intracranial traumatic causes would have been sought in view of the alcohol history and not knowing about this effect of selective serotonin reuptake inhibitors.

Mydriasis in association with paroxetine has been reported to the Committee on Safety of Medicines on 21 occasions, but it seems that the noticeably asymmetrical mydriasis noted in these two cases has not previously been reported.

Parotitis induced by chlormethiazole

Drs X Bosch, M Sans, F Martinez-Orozco, and A Urbano-Marquez (Hospital Clinic, Barcelona 08036, Spain) write: Chlormethiazole is a sedative and hypnotic that is widely used in treating and preventing symptoms of acute alcohol withdrawal.[1] We describe a case of bilateral parotitis after chlormethiazole treatment.

A 48 year old man presented with a history of epigastric pain and haematemesis for three days. He had regularly drunk 300 g ethanol a day in the previous year, mainly in the form of red wine and whisky. He had an enlarged liver, but otherwise physical examination showed nothing abnormal. He had a mild macrocytic anaemia (haemoglobin 115 g, mean corpuscular volume 106) and an increased concentration of γ-glutamyltransferase (122 U/l). Endoscopy showed severe oesophagitis and a hiatus hernia. We started treatment with intravenous fluids and ranitidine, together with oral chlormethiazole (384 mg four times daily).

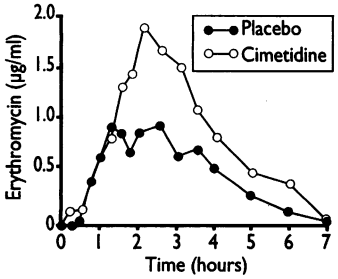
One day after admission the patient developed a painful bilateral enlargement of the parotid glands. He explained that during the previous day he had experienced a burning sensation in his parotid glands after taking each dose of chlormethiazole. We immediately stopped the chlormethiazole. Two days after admission the parotid enlargement had disappeared and another dose of chlormethiazole (364 mg) was given. Twenty minutes later the patient complained of a dry mouth and had a painful bilateral swelling of the parotid glands. He had no fever, rash, or eosinophilia. The swelling resolved over six hours. Chlormethiazole was stopped and diazepam was given, without any side effects.

The association in time and positive rechallenge strongly suggest that chlormethiazole was responsible for the development of parotitis in this patient. Parotid swelling has been reported as an adverse reaction to several drugs such as iodide compounds, phenylbutazone, methyldopa, nifedipine, and nicardipine. Parotid pain without enlargement of the salivary glands has been reported in patients treated with antihypertensive drugs.[2-5] To our knowledge, this is the first published report of chlormethiazole causing swelling of the parotid glands.

1 Dollery C, ed. *Therapeutic drugs.* Vol 1. Edinburgh: Churchill Livingstone, 1991. C184-8.
2 Pellinen T. Nitrofurantoin-induced parotitis. *BMJ* 1982;285:344.
3 Mardh PA, Balfrage I, Naversten E. Sialadenitis following treatment with alpha-methyldopa. *Acta Med Scand* 1974;195: 333-5.
4 Chen JH, Ottolenghi P, Distenfeld A. Oxyphenbutazone-induced sialadenitis. *JAMA* 1977;238:1399.
5 Bosch X, Sobrino J, Lopez-Soto A, Urbano-Marquez A. Parotitis due to nicardipine. *BMJ* 1992;304:882.

Erythromycin deafness and cimetidine treatment

Drs N Mogford and A Pallett and Professor C George (Southampton General Hospital, Southampton SO9 4XY) write: A 64 year old woman was admitted with cough, dyspnoea, and pleuritic pain. She was taking methyldopa 125 mg and co-amilofruse once daily with propranolol 10 mg each morning and 40 mg at night for hypertension, and ranitidine 150 mg twice daily for a duodenal ulcer. Her blood pressure was 80/50 mm Hg and her respiratory rate 28/minute. Consolidation of the right lung was confirmed by chest radiography. Her white cell count was $26{\cdot}2\times10^9$/l and serum creatinine concentration 158 μmol/l. Later *Streptococcus milleri* was isolated from her sputum.



Mean serum concentrations of erythromycin in eight healthy volunteers after erythromycin stearate 250 mg given orally with placebo or cimetidine

All antihypertensive treatment was stopped, and she began taking oral amoxycillin 500 mg three times daily and erythromycin stearate 1g four times daily for her atypical pneumonia. Cimetidine (400 mg at night) was substituted for ranitidine. After two days she experienced "fuzzy hearing" and erythromycin was withdrawn. Audiography showed bilateral hearing loss of 40-60 dB at frequencies of 0·25-8 kHz; hearing returned to normal five days after erythromycin was withdrawn.

Since cimetidine inhibits the N-demethylation of erythromycin in vitro,[1] we investigated a possible interaction in six healthy men and two women aged 19-23. They received in random order on day 1 either cimetidine 400 mg twice daily or placebo, and on day 2 erythromycin stearate 250 mg plus cimetidine 400 mg or placebo. Cimetidine did not interfere with the bioassay but increased the area under the serum concentration-time curve of erythromycin by 73% and the median value from 2·97 to 5·06 μg/ml.h ($P<0{\cdot}05$) by Wilcoxon rank sum test (figure).

Our case is typical of the 47 cases of erythromycin induced deafness reported to the Committee on Safety of Medicines since 1963: our patient received erythromycin in large doses and had renal impairment and characteristic audiograms. In our case, however, cimetidine is considered to have aggravated the deafness by increasing the serum and otic concentrations of erythromycin.

1 Watkins PB, Wrighton SA, Shuetz EG, Molowa DT, Guzelian PS. Identification of glucocorticoid inducible cytochrome P450 in intestinal mucosa of rats and man. *J Clin Invest* 1987;80:1029-36.