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Peptic ulcer, cimetidine, and motor neurone disease – a record linkage study

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Abstract

A previous cohort study suggested that there might be an association between use of cimetidine and motor neurone disease. The Oxford Record Linkage Study was used to explore this hypothesis. In the analysis the presence of a peptic ulcer in patients after 1976 was taken as a proxy for cimetidine (and ranitidine) use. The past history of 540 patients with motor neurone disease in this period was compared with that of 1370 patients with multiple sclerosis (neurological controls) and over 240 000 control patients with a variety of other conditions. Among those with motor neurone disease, five had been previously admitted to hospital with peptic ulcer in comparison with an expected number of 7·4 (morbidity ratio 0·68, 95% confidence interval: 0·2 to 1·6). The corresponding figures for those with multiple sclerosis were 12 and 9·7 respectively (morbidity ratio 1·24, 95% confidence interval: 0·6 to 2·2). This study provides some evidence against the possibility that cimetidine (and ranitidine) are related to motor neurone disease.

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Research staff based at Glasgow, Nottingham, Oxford, and Portsmouth have, for many years, been following the pattern of mortality in a cohort of 10 000 takers of cimetidine.[1] In the latest report to become available, dealing with mortality at 10 years, eight deaths were certified as being from motor neurone disease while only three such deaths were expected from national rates.[2] This gave a relative risk of 2·6 (95% confidence interval: 1·1 to 5·1). The authors noted that one of the eight deaths had been recorded as being from motor neurone disease even though the patient had died from a myelopathy secondary to severe cervical spondylosis. It was also noted, however, that in most of the cases of motor neurone disease there was a 'clear history of long-term use of cimetidine' and that 'this observation might warrant further study'.

We judged this to be a potentially important finding in view of the extremely widespread use of cimetidine. We therefore used the Oxford Record Linkage Study[3] to shed some light on any association. The Oxford Record Linkage Study does not collect information about prescriptions but data are collected about admissions to hospital for peptic ulcer. We considered that it would be reasonable to take peptic ulcer in people admitted after 1976 as a proxy for cimetidine use (bearing in mind that cimetidine has only been available since then) and to see if peptic ulcer was commoner in people with motor neurone disease than in others.

Population and method

The Oxford Record Linkage Study abstracts and organises records of hospital inpatient care and death certificates collected in a geographically defined population, such that records of successive events for the same person can be linked together.[3,4] Two of the eight districts in the Oxford Region were covered by data collected from 1968–86 and a further four from 1974–86 (total populations covered in the two periods: 850 000 and 1·9 million people).

Patients' records with a diagnosis of motor neurone disease at any position on the record were identified. Records of patients with multiple sclerosis were selected as a neurological comparison group. A mixed group of controls was also selected, which consisted of people with admissions for a broad range of elective operative procedures (excluding operations for peptic ulcer), appendicectomy, fractures, and other injuries as the main diagnosis on the hospital record. Records of previous admission for peptic ulcer were sought for people in the case and the comparison groups. Anyone who had both a case and a control diagnosis was excluded from the analysis. The data set was subdivided into people whose first recorded case or control event occurred in 1976 or before and those whose first recorded events occurred between 1977–86. The data set was then stratified in the analysis by 5 year age groups, sex, calendar year of first diagnosis of case or control event, and district of residence at first diagnosis. The rates of previous admission for peptic ulcer in each stratum in the control group were used to calculate the number of people in each stratum in the motor neurone disease and multiple sclerosis groups who would have been 'expected' to have a previous admis-

Number of patients in the three groups: control, motor neurone disease, and multiple sclerosis; the observed (Obs) and expected (Exp) numbers of patients with previous admissions for peptic ulcer with their ratios and 95% confidence interval (CI)

Year of index event	*Controls*		*Motor neurone disease*					*Multiple sclerosis*				
	Total	*Obs*	*Total*	*Obs*	*Exp*	*Ratio*	*95% CI*	*Total*	*Obs*	*Exp*	*Ratio*	*95% CI*
1968–76	118 583	309	267	1	1·84	0·54	0·01 to 3·03	770	2	2·76	0·73	0·09 to 2·62
1977–86	240 258	1221	540	5	7·38	0·68	0·22 to 1·58	1370	12	9·65	1·24	0·64 to 2·17
1968–86	358 841	1530	807	6	9·23	0·65	0·24 to 1·42	2140	14	12·41	1·13	0·62 to 1·89

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sion for peptic ulcer. The expected numbers in each stratum were then summed to give an overall expected number; and this was compared with the observed number of subjects with motor neurone disease and multiple sclerosis who had a previous admission for peptic ulcer. Confidence intervals for the ratio of observed to expected numbers of patients with previous peptic ulcer were calculated from published tables for Poisson distributions.[5]

Results

The Table gives the findings which, for cases and controls after 1976, includes 540 cases of motor neurone disease, 1370 of multiple sclerosis, and 240 258 controls. It can be seen that patients with multiple sclerosis had a slight excess of previous admissions for peptic ulcer (morbidity ratio 1·24) and patients with motor neurone disease had slightly fewer admissions than expected (morbidity ratio 0·68). The ratio did not differ significantly from one for either disease. We also examined data for the period before the introduction of cimetidine (1968–76). The contrast between the two periods was weak because of the small amount of data in the earlier period. None the less, nothing untoward was detectable.

Discussion

The finding that stimulated this study was generated in the context of multiple significance testing across a wide range of diseases in relation to cimetidine. For this reason it may have been spurious but worth further study. The findings presented here can provide only indirect evidence about any possible adverse effect of cimetidine on motor neurone disease. None the less, during the period under review, it became more or less routine to treat peptic ulcers with cimetidine (or ranitidine) and the absence of any relation between peptic ulcer and motor neurone disease offers some reassurance. The other difficulty, of course, is that the observed and expected numbers are rather small (despite the large number of cases and controls) and the study is therefore somewhat lacking in statistical power. On the evidence of this study it is unlikely that any relative risk could be as large as twofold, but we cannot discount a 50% increase in risk.

It has been suggested (in the era before cimetidine was introduced) that peptic ulcer, or some factor associated with its treatment, might itself be a risk factor for motor neurone disease.[6] Our results offer some reassurance on this issue as well.

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