Female breast engorgement on ranitidine – A case report

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Summary

A 60 year old woman with chronic duodenal ulcer not responding to Cimetidine, was changed to Ranitidine. She had symptomatic improvement, but had bilateral breast engorgement and tenderness for which treatment was discontinued. A therapeutic trial on a second occasion had the same side effect which came on more rapidly and quickly. This complication in such severe form and recurrence on rechallenge requiring withdrawal of drug was observed for the first time with any H2 receptor antagonist.

Key words: Breast engorgement, Ranitidine, Cimetidine.

Introduction

Over a decade ago, Cimetidine was the first drug to find widespread clinical application as competitive antagonist of Histamine at H2 receptor site. After a few years, Ranitidine was available. Invention of this group of drug has been a major breakthrough in treatment of peptic ulcer diseases. The previous generation of these drugs were found unsuitable for clinical use because Buriamamide[1] had variable potency and irregular absorption while Metiamide[2] caused serious side effects e.g. aganulocytosis.

As Cimetidine[3,4,5] binds with other sites as well, serious side effects may occur due to interactions. For example, inhibition of enzymes at hepatic oxygenase system due to binding with Cytochrome P 450 which potentiates the action of some drug like Diazepam, warfarin etc. Cimetidine also binds at the 'Androgen receptor' which may cause gynacomastia.

Ranitidine[6,7,8] differs from Cimetidine in having substituted furan instead of imidazole and has a different side chain. Ranitidine does not bind at the additional sites and therefore is less likely to cause serious side effects. However, both drugs have similar half life in peripheral circulation (about two hours) and duration of action.

Case history

In April 1982, a 60 year old female was referred by a psychiatrist for management of her chronic recurrent dyspepsia. She had a long history and strong family history of duodenal ulcer, confirmed on a number of occasions by barium meal study, the last being two years ago. Since then, she was on long term Cimetidine therapy. She was treated by psychiatrist for her agitated depression. Her antidepressant was changed from Doxepin (Sinequan) to Mianserin (Bolvidon) as her depression deteriorated recently.

On examination, she had epigastric tenderness. Systemic examination and all screening tests were normal. Her treatment with Cimetidine was stopped and Ranitidine was commenced on clinical grounds. During her follow up a month later, improvement of her dyspeptic symptoms were noted but she felt heaviness and pain in both breasts about two weeks following therapy. Clinically, she had bilateral swelling of breast particularly tense in the areolar and periareolar regions with tenderness. She had no history of chronic mastitis and she received no other new drugs.

The patient felt very strongly that this complication was due to Ranitidine but we thought that was unlikely. Mianserin was stopped and she was advised not to go back on Doxepin,[9] as both drugs have been reported to cause similar breast problems though rarely. In view of her symptomatic improvement, Ranitidine was continued. Unfortunately, within a few days her breast symptoms worsened progressly and became so unbearable that she discontinued Rani tidine herself. The breasts became normal within a week.

During her attendance in the psychiatric clinic, as she had considerable symptoms of peptic ulcer, the psychiatrist decided to try Ranitidine again. No other drug was prescribed from psychiatric or medical clinic. On this occasion, her breast swelling and tenderness came back within six hours and deteriorated further within a few days. Therefore, the treatment had to be discontinued and the breast problems subsided again completely.

When she came for review in August 1982, we decided to reassess the diagnosis by endoscopy before considering any further definitive therapy. Gastroscopy showed deformed duodenum but no ulcer. She had a small hiatus hernia and mild oesophagitis for which she was treated with regular antacids only. On subsequent follow up in medical clinic for next two years her symptoms were reasonably controlled. She was discharged from the clinic to the care of her general practitioner where she has been on regular follow up. Since then, she had no further recurrence of the breast symptoms after stopping Ranitidine.

Discussion

Because of her long history, family history and clinical findings suggestive of duodenal ulcer, a definitive therapy was indicated for her. Ranitidine was chosen[10,11] because it is likely to be effective in Cimetidine failed cases; it is more potent and has less side effects for reasons mentioned above. It was very unusual to see side effects with Ranitidine when patient tolerated Cimetidine for a long period. This patient's breast signs following commencement of therapy and in particular, reappearance of the signs in shorter time and in more acute form after a rechallenge with Ranitidine, proves convincingly that the Ranitidine was the offending agent. However, the mechanism leading to this complication remains uncertain.

There was no previous incidence of such a side effect on female breast recorded by the manufacturer or in the list of adverse reaction with Ranitidine documented by the Committee of Safety of Medicine, U.K. recorded at that time. Since then, breast tenderness and swelling were noted in some patients whilst on treatment with Ranitidine in several studies[12,13,14] over past five years. However these symptoms were not marked, subsided spontaneously and all patients completed Ranitidine therapy. Recurrence of breast tenderness, swelling and engorgement in very severe form and in shorter duration necessitating discontinuation of therapy were not seen in any of these studies.

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References

1. Wyllie JH. On action of Buriamamide. Lancet 1972; 2: 1117–8.
2. Feldman EJ and Isenberg JI. Metiamide causing agranulocytosis. New Eng J Med. 1976; 295: 1178.
3. Desmond PV, Shaw R, Westwood B et al. Comparison on the effect of Ranitidine and Cimetidine on hepatic drug metabolism. Aust NZ J Med 1983; 13: 314–7.
4. McGuigan JE. A consideration of the adverse effect of Cimetidine. Gastroenterology 1981: 80: 181–4.
5. Feely J. Interaction of Cimetidine with other drugs. South Med J 1983; 76: 753.
6. Penston J and Wormsley KG. Adverse reactions and interactions with H2 receptor antagonists. Med Toxicology 1986; 1: 192.
7. Mitchard M, Harris A, Mullinger BM. Ranitidine interaction, a literature review Pharmac Thera 1987; 132: 293–319.
8. Misiewicz JJ, Sewing KFr. First international symposium on Ranitidine. Scan J Gastroent; 16: suppl. 69.
9. Martindale, The Extra Pharmacoepia. On adverse effect of Tricyclicantidepressant, Doxepin; 28th. ed., 1982: 110–118
10. Mohammed R, Mitcheland KG and Mackay G. The treatment of Cimetidine resistant cases with Ranitidine hydrochloride, a new histamine H2 receptor antagonist. Curr Med Res Opin 1981; 7(8): 523–5.
11. L Witzel and E Wolberg. Peptic ulcer healing with Ranitidine in Cimetidine resistant cases. Lancet 1982; 27: 1224.
12. Leroux P, Farley A. Effect of Ranitidine on healing of peptic ulcer, A 2-month study. Am J Gastroent 1983; 78 (8): 227–9.
13 Ireland A, ColinJones DG, Gear P et al. Ranitidine 150mg twice daily vs 300mg nightly in the treatment of duodenal ulcers. Lancet 1984; 32: 274–5.
14. Farley A, Levisque D, Pare P et al. A comparative trial of Ranitidine 300mg at night with Ranitidine 150mg twice daily in the treatment of duodenal and gastric ulcer. Am J Gastroent 1985; 80(9): 665–8.