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Comments and Critique

'. . .Setron': Are 5-HT$_3$ Receptor Antagonists Different?

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GRANISETRON, ONDANSETRON, tropisetron and soon dolasetron, to be followed by other 'setrons', are changing the clinical approach to cancer therapy (and other therapy) related emesis. There is no doubt about their efficacy in controlling acute (as opposed to delayed) emesis, and sound discussions about cost–benefit issues should now enable clinicians and administrators to reach the correct decisions [1]. Preclinical studies have shown that there are some differences between these agents. Their antagonist activity against some receptors differs, although this difference may not be significant in clinical terms [2]. There are clear differences in potency, which indicate that, for example, granisetron is ten times as potent as ondansetron [3]. Therefore, the debate about the correct dose to be used is important, and everyone has noticed that a European and an American study differ in their conclusion about the recommended dose of ondansetron to prevent cisplatin-induced emesis [4, 5]. Careful reading of both articles reveals that the analyses have been conducted in different ways, and differences in the emetogenic potential of the other drugs combined with cisplatin, along with different cisplatin doses, may explain these divergent views. It may be, however, that the addition of corticosteroids to 5-HT$_3$ receptor antagonists will allow the use of lower doses of these expensive agents, without loss in antiemetic efficacy, even among patients subjected to really highly emetogenic chemotherapy. This is suggested by many studies, and the Italian group has demonstrated that a combination of medium doses of ondansetron along with dexamethasone is superior to the 'gold standard' of the past, a metoclopramide–steroid combination [6]. This issue of the *European Journal of Cancer* contains the first peer-reviewed publication of a comparative clinical study between ondansetron 8 mg, tropisetron 5 mg and granisetron 3 mg, given intravenously once (pp. 1669–1672). The patient population was mainly female, undergoing 'moderately' emetogenic chemotherapy for breast cancer and other cancers. The design is interesting in that patients served as their own controls receiving one of the three agents at each subsequent chemotherapy. It has several shortcomings. It is open and not blind, and nausea was not recorded. However, the data are sufficiently convincing for the reviewers and editors to have accepted this publication. As the authors correctly point out, the most important difference they observed is the small amount of failures with granisetron, which explains patient preference. However, clinically the most important fact should be total control, i.e. absence of vomiting AND nausea, which they did not look for. Another possible bias could be a possible difference in emetogenicity between the three arms of the study on cycle 1; however, this does not detract from the expressed patient preference. Another study comparing granisetron 3 mg, ondansetron 8 mg or 32 mg has been recently presented at a Glaxo Satellite Symposium, April 28, 1993, at 'Eurocancer' in Paris. This multicentre study comprised 496 patients in 42 centres, treated with cisplatin (> 50 mg/m^2)-based chemotherapy. The study was 'investigator and patient blind': the nurse preparing the materials (but not treating the patient) was not blinded. Patients completed a 24-h self-assessment questionnaire. There were no differences in control of emesis (51 to 59% complete control) or nausea (47 to 56% complete control), over the 24 h of observation. Adverse events related to the drug were not statistically different, and were minor (headaches mainly, in 8 to 13% of the study population). Why is there no difference between these two agents in this study when there is in the study published in this journal? Many confounding factors can affect the outcome of an antiemetic study. Neither studies are ideal in their design, and the one presented in Paris has yet to be published with sufficient detail. Were there differences when the emetogenic potential was high (i.e. cisplatin doses above 100 mg/m^2; cisplatin in some combinations)? Such a difference between the two doses of ondansetron has been apparent in the other studies. The final answer will not come from these data. Other studies are underway, and may or may not show a difference. Possibly all studies are too small to give the real answer, but a valid meta-analysis will probably not be possible for a long time. Many will argue that these differences are minor, and might disappear if corticosteroids are added to 5-HT$_3$ receptor antagonists. This may be true, but it remains to be proven, and I would certainly not want to be among the 10% who were not protected because a 'non-significantly' minor protection was offered.

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