

Nonionic contrast media: a bargain for some, a burden for many

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Drs. Gafni and Zylak raise two important issues concerning our paper on the cost-utility ratio of nonionic radiologic contrast media:¹ the disutility of quality-adjusted life-years (QALYs) associated with very minor and minor side effects and the use of QALYs to measure the clinical effects. We believe that the former issue is now an important component of the policy debate going on in Canadian institutions and that the latter is an important issue for researchers in the field of decision analysis. We address the former in this reply.

At the time the decision was made in Ontario to convert from the old to the new contrast media we felt that most of the concern about contrast agents was focused on safety related to very major reactions and death. This was almost certainly a result of two deaths in Ontario that led to coroner's inquests. Because of the concern we structured our analysis to examine such outcomes. We believed that we were biasing the analysis very heavily in favour of the new media by assuming that they would reduce the risk of death 10-fold. As far as we are aware there is no published evidence to show that the new media reduce the risk of death by that amount. Moreover, the studies of Katayama and associates,² Palmer,³ and Wolf, Arunson and Cross⁴ showed a reduction of three to six times in the risk of reactions requiring physician intervention but no reduction in death rates. This is partly because the baseline risk of death from ionic contrast media has fortunately declined. It now appears that radiologists are more concerned with the very minor and minor side effects and the benefit the new agents offer in this respect. It is important, therefore, to consider this issue more fully, as Gafni and Zylak have done.

We still believe that the framework for the analysis should separate the low-risk and high-risk patients and procedures. There are data showing that the benefits of the new agents are greater (i.e., lower risk of reactions) among patients at high risk (e.g., because of a previous reaction) and among those

who are at high risk for hemodynamic complications (e.g., those undergoing cardiac catheterization). The incremental cost-utility ratios cited by Gafni and Zylak concern the complete conversion from the old to the new agents for all patients in one step. The correct analytic strategy would be first to examine the incremental cost-utility ratio derived from the delivery of the new agents only to high-risk patients and the continuing use of the old agents for low-risk patients and then to calculate the incremental cost-utility ratio of moving from this "selective use" policy to one of universal availability. We recalculated the marginal cost-effectiveness ratios for using new contrast media only among patients at high risk (30% of general radiology patients) and among those at low risk (the remaining 70%) using the healthy years equivalent (HYE) with the same assumptions that Gafni and Zylak make.

The complete results are as follows: for administering nonionic contrast media only to patients at high risk the marginal cost per HYE gained is \$8400; for treating the low-risk patients the marginal cost per HYE gained is \$121 000. The marginal cost-effectiveness ratio for treating all patients is \$25 000 per HYE gained, as reported by Gafni and Zylak.

The treatment of low-risk patients remains much less efficient than the treatment of only high-risk patients. The treatment of only high-risk patients is an even more efficient strategy in the new analysis. This is to be expected since the new assumptions favour nonionic contrast media.

The results from our recalculation and from our original paper should be interpreted very carefully. The probabilities used for occurrence of reactions and relative risks with the new contrast media were determined on the basis of data available at the time of the original analysis. New data are quite different with respect to mortality rates, reaction rates and risk levels across the different risk groups.

We agree with Gafni and Zylak that a study measuring actual patient preferences would be the

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ideal basis for an analysis such as this. A pilot study to measure preferences for the two forms of contrast media showed inconsistent results (V.G.: unpublished data). The main reason for this is the difficulty people have in properly integrating information about such small levels of risk and changes to these risks. The methods proposed by Gafni and Zylak would in all likelihood be even more difficult to implement. However, we hope that research into this important area will continue.

We compared our results with those of other economic evaluations using QALYs. However, since the HYE is a different unit of outcome we are uncertain that such comparisons can readily be made. We believe that Gafni and Zylak should estimate HYE's gained for other health programs and then recalculate the cost-effectiveness ratios for those programs before making comparisons.

In conclusion, although the assumptions proposed by Gafni and Zylak make this investment of resources appear more attractive than our previous analysis, the ratio associated with low-risk patients still suggests that the use of the new, more expensive agents requires more resources per unit of benefit than most of the other interventions that have been

evaluated in a similar manner. In addition, since many health care interventions have not been subject to this kind of analysis we believe that relative to the use of all Canadian health care resources the use of nonionic agents may not be the least attractive use of resources. For institutions to use these criteria to help set priorities the cost-utility ratio of other interventions should also be measured. We have heard that with more competition on the market the price of the new agents may be substantially reduced. This would require another evaluation of the cost-utility ratio, which could further improve the image of the new contrast agents.

References

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PRESCRIBING INFORMATION

ZANTAC TABLETS (ranitidine hydrochloride)

Pharmacological Classification

Histamine H₂ - receptor antagonist

Indications and Clinical Use

Zantac Tablets are indicated for the treatment of all conditions where a controlled reduction of gastric secretion is required for the rapid relief of pain and/or ulcer healing. These include duodenal ulcer, benign gastric ulcer and reflux oesophagitis.

Contraindications - Zantac is contraindicated for patients known to have hypersensitivity to the drug.
Warnings - Gastric ulcer - Treatment with a histamine H₂ - antagonist may mask symptoms associated with carcinoma of the stomach and therefore may delay diagnosis of the condition. Accordingly, where gastric ulcer is suspected the possibility of malignancy should be excluded before therapy with Zantac is instituted.

Precautions - Use in pregnancy and nursing mothers - The safety of Zantac in the treatment of conditions where a controlled reduction of gastric secretion is required during pregnancy has not been established. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to Zantac. If the administration of Zantac is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and to the foetus. Ranitidine is secreted in breast milk in lactating mothers but the clinical significance of this has not been fully evaluated.

Use in impaired renal function - Ranitidine is excreted via the kidney and in the presence of severe renal impairment plasma levels of ranitidine are increased and prolonged. Accordingly, in the presence of severe renal impairment clinicians may wish to reduce the dose by one half.

Children - Experience with Zantac Tablets in children is limited and such use has not been fully evaluated in clinical studies. It has however been used successfully in children aged 8-18 years in doses up to 150 mg twice daily without adverse effect.

Interactions with other drugs - Although ranitidine has been reported to bind weakly to cytochrome P450 in vitro, recommended doses to the drug do not inhibit the action of the cytochrome P450-linked oxygenase in the liver. There are conflicting reports in the literature about possible interactions between ranitidine and several drugs, the clinical significance of these reports has not been substantiated. Amongst the drugs studied were warfarin, diazepam, metoprolol and nifedipine.

If high doses (2g) of sucralfate are co-administered with ranitidine the absorption of the latter may be reduced. This effect is not seen if sucralfate is taken after an interval of 2 hours.

Adverse Reactions - Headache, sometimes severe, rash, dizziness, constipation, diarrhoea and nausea have been reported in a very small proportion of drug-treated patients but these also occurred in patients receiving placebo. A few patients on re-challenge with Zantac have had a recurrence of skin rash, headache or dizziness. Rare reports of bradycardia have occurred. Rare cases of reversible mental confusion and hallucinations have been reported, predominantly in severely ill and elderly patients. There have been a few reports of reversible blurred vision suggestive of a change in accommodation.

Some increases in serum transaminases and gamma-glutamyl transpeptidase have been reported which have returned to normal either on continued treatment or on stopping Zantac. In placebo controlled studies involving nearly 2,500 patients, there was no difference between the incidence of elevations of SGOT and/or SGPT values in the Zantac treated or placebo treated groups. There have been occasional reports of reversible hepatitis (hepatocellular, hepatocellular or mixed) with or without jaundice. Hypersensitivity reactions (urticaria, angioneurotic oedema, bronchospasm, hypotension) have been seen rarely following the parenteral and oral administration of Zantac. These reactions have occasionally occurred after a single dose.

Reversible blood count changes (leucopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia sometimes with marrow hypoplasia have been reported. Other haematological and renal laboratory tests have not revealed any drug related abnormalities. No clinically significant interference with endocrine or gonadal function has been reported. There have

been a few reports of breast symptoms (swelling and/or discomfort) in men taking ranitidine; some cases have resolved on continued treatment.

Symptoms and Treatment of Overdosage - No particular problems are expected following overdosage with Zantac. Symptomatic and supportive therapy should be given as appropriate. If need be, the drug may be removed from the plasma by haemodialysis.

Dosage and Administration - Adults: Duodenal ulceration, benign gastric ulceration, or reflux oesophagitis: 300 mg once daily at bedtime.

It is not necessary to time the dose in relation to meals. In most cases of duodenal ulcer and benign gastric ulcer, healing will occur in four weeks. In the small number of patients whose ulcers may not have fully healed, these are likely to respond to a further course of treatment.

Patients who have responded to this short term therapy, particularly those with a history of recurrent ulcer, may usefully have extended maintenance treatment at a reduced dosage of one 150 mg tablet at bedtime.

To help in the management of reflux oesophagitis, the recommended course of treatment is one 300 mg tablet once daily at bedtime or one 150 mg tablet twice daily for up to 8 weeks.

Children: Experience with Zantac in children is limited and it has not been fully evaluated in clinical studies - see **Precautions**.

Availability - Zantac Tablets are available as white film-coated tablets engraved ZANTAC 150 on one face and GLAXO on the other, containing 150 mg ranitidine (as the hydrochloride), in packs of 30 and 60 tablets.

Zantac Tablets are also available as white, capsule shaped, film-coated tablets engraved ZANTAC 300 on one face and GLAXO on the other, containing 300 mg ranitidine (as the hydrochloride), in packs of 30 tablets.

Zantac Injection is available as 2 mL ampoules each containing 50 mg ranitidine (as the hydrochloride) in 2 mL solution for intravenous or intramuscular administration. Packages of 10 ampoules. Product Monograph available on request.

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