Denial of effective treatment and poor quality of clinical information in placebo controlled trials of ondansetron for postoperative nausea and vomiting: a review of published trials

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Abstract

Objective—To determine how many patients were deprived of treatment by being given placebo as comparator in trials of ondansetron for postoperative nausea and vomiting.

Design—Review of published trials of ondansetron during 1991 to July 1994.

Setting—Medline search in a university department of anaesthesia.

Subjects—8806 patients who had been included in 18 indexed placebo controlled trials of ondansetron as prophylaxis against or treatment of postoperative nausea and vomiting.

Results—Five studies (1236 patients) had been published by July 1992. All were placebo controlled trials. By July 1994, 8806 patients had been included in 18 indexed placebo controlled studies of prophylaxis or treatment. Only 462 patients had been in studies that compared ondansetron with other drugs, and there were no indexed comparative trials of treatment of nausea and vomiting. Roughly 2180 patients had been given placebo as prophylaxis and 440 had been given placebo when already experiencing postoperative nausea or vomiting.

Conclusions—Around 2620 patients in the reviewed studies were denied existing drugs, which, though not completely effective or without side effects, do bring some relief from postoperative nausea and vomiting. Drug regulatory bodies should collaborate with drug companies to ensure better comparison of new with established drugs. This would avoid placebos being given to more than the fewest patients necessary to confirm effect and would allow doctors to be informed more quickly about relative efficacies.

Introduction

Advertisements for the 5HT₃ receptor antagonist ondansetron "Making history of postoperative nausea and vomiting" were published in the *BMJ* from July 1992. In one advertisement in the first issue of 1993 five references were given. All referred to studies in oncology. We wanted to know what trials on postoperative nausea and vomiting had been published by the beginning of the campaign and what trials had been published since. Ondansetron may be given as treatment of postoperative nausea and vomiting or as prophylaxis against it.

It became clear that most of the trials were comparisons with placebo. We therefore concentrated on analysing the use of placebo. We wanted to know the number of patients denied more effective treatment and to consider the value of data from trials of a drug not tested against a comparator.

Method and results

In July 1994 we ran a Medline search on "ondansetron" and "postoperative complications" via the PaperChase service of Compuserve, current to May 1994. We checked the June and July 1994 issues of the locally available anaesthesia journals—*British Journal*

of Anaesthesia; *Anaesthesia*; *Anesthesia and Analgesia*; *Anesthesiology*; and *Canadian Journal of Anaesthesia*. We noted the number of patients, what the comparison groups were given, the number of patients given placebo, the route of administration, and whether the trial was of prophylaxis or of treatment. We did not attempt to assess formally the methods or other aspects of the validity of the trials.

We traced 26 publications (table). In the five that predated the advertising campaign, 316 patients in three studies received placebo as prophylaxis and 54 in two studies received placebo as treatment for sickness. In no study was ondansetron compared with an active drug.

By July 1994, 8806 patients had been included in 18 placebo controlled trials, whether of prophylaxis or of treatment. Of these patients, roughly 2180 had received placebo as prophylaxis and 440 had received placebo as treatment. A total of 462 patients had been included in four trials of comparisons with active drugs. These trials, however, were of prophylaxis only and two had a placebo arm. There were no published trials of ondansetron compared with active drugs for treatment.

Calculating how many patients received placebo was not always simple. In one study the summary described 1000 patients being entered into the trial. The text gave 1022, which was the number needing treatment out of the 2812 who gave consent. However, because of protocol violations, findings from 886 patients were analysed.¹

Discussion

We were concerned not whether ondansetron was the best treatment for postoperative nausea and vomiting but whether the published trials could enable any decision. We may have missed some studies, particularly those published by July 1994 as abstracts only, but we did not miss any that were readily available to the clinicians who would have seen the advertising campaign. There was almost no useful, readily obtainable information by the start of the campaign. There was little more at the time of our survey.

Many workers think that unless a condition is trivial an active treatment should be given if there is one.^{2,3} A comparative study of ondansetron was published in 1992,⁴ so other early trials could have used comparator drugs.

Some anaesthetists do not give prophylaxis against postoperative nausea and vomiting. Hence it is certainly less reprehensible to test against placebo for prophylaxis than it is to test against placebo for treatment. But if a new antiemetic is compared only with placebo clinical decisions about which drug to use cannot be based on evidence. The lack of standardisation in previous studies makes comparisons difficult⁵ but any trial without an active treatment arm fails to provide that evidence. The investigators acknowledged that effective treatments exist by allowing rescue antiemesis.

Over 2000 patients were denied effective prophylaxis in these studies. But far worse, over 400 patients

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BMJ 1995;311:844-6

Year study published	Reference	No of patients	No given placebo	Comparators and dose of ondansetron (mg)†	Route	Whether trial of treatment or trial of prophylaxis
<i>Before advertising campaign</i>						
1991	Leeser and Lip (June) ²⁰	84	42	P,16	Oral	Prophylaxis
	Larijani <i>et al</i> (Sep) ²¹	36	18	P,8	Intravenous	Treatment
	Bodner and White (Sep) ²²	71	36	P,8	Intravenous	Treatment
1992	Kenny <i>et al</i> (May) ²³	995	249	P,1,8,16	Oral	Prophylaxis
	Dershwitz <i>et al</i> (Jul) ²⁴	50	25‡	P,8	Intravenous	Prophylaxis
<i>After advertising campaign</i>						
	Alon and Himmelseher (Oct) ⁴	66	0	D,M,8	Intravenous	Prophylaxis
	Kovac <i>et al</i> (Nov) ²⁵	580	142	P,1,4,8	Intravenous	Prophylaxis
	Helmert (Nov) ²⁶	995	—	P,1,8,16	Oral	Prophylaxis
	Helmert (Nov) ²⁶	243	120	P,8	Oral	Prophylaxis
	Du Pen <i>et al</i> (Nov) ²⁷	500	129	P,1,4,8	Intravenous	Treatment
	Bouly <i>et al</i> (May) ²⁸	60	30	P,8	Oral	Prophylaxis
1993	McKenzie <i>et al</i> (Jan) ²⁹	207	103‡	P,8	Intravenous	Prophylaxis
	Sung <i>et al</i> (Jan) ³⁰	180	90‡	P,8	Intravenous	Prophylaxis
	Scuderi <i>et al</i> (Jan) ³¹	500	—	P,1,4,8	Intravenous	Treatment
	McKenzie <i>et al</i> (Jan) ³²	580	—	P,1,4,8	Intravenous	Prophylaxis
	Dupeyron <i>et al</i> (Mar) ⁵	243	—	P,8	Oral	Prophylaxis
	Helmert <i>et al</i> (Dec) ³³	923	235	P,4,8,16	Intravenous	Prophylactic
	Raphael and Norton (Dec) ⁴	123	0	M,4	Intravenous	Prophylaxis
1994	Pearman (Jan) ³⁴	1169	282	P,4,8	Oral	Prophylaxis
	Pearman (Jan) ³⁵	468	223	P,4	Oral	Prophylaxis
	Rust and Cohen (Jan) ³⁶	813	204	P,4,8,16	Oral	Prophylaxis
	Rust and Cohen (Jan) ³⁶	1345	327	P,4,8,16	Oral	Prophylaxis
	Claybon (Jan) ¹	1022	225‡	P,1,4,8	Intravenous	Treatment
	Malins <i>et al</i> (Feb) ³⁷	153	50	P,M,4	Oral	Prophylaxis
	Litman <i>et al</i> (Mar) ³⁸	60	30	P,8	Intravenous	Prophylaxis
	Gan <i>et al</i> (May) ³⁹	120	40	P,D,4	Intravenous	Prophylaxis

†P=Placebo. D=Droperidol. M=Metoclopramide. ‡Estimated number. —=Duplicate report.

already experiencing symptoms were denied treatment. It is difficult not to conclude that this was an example of industry failing to seek information that would allow true comparisons with rival products.^{6,7} The company also allowed its investigators to repeat in three journal supplements between 1992 and 1994 that ondansetron was better than placebo—but that the results of comparative trials were awaited.⁸⁻¹⁰ The problems of sponsored journal supplements are well known,¹¹⁻¹³ and there is the contrast between an independent reviewer's conclusion that "ondansetron's exact role in the perioperative setting still remains to be determined"¹⁴ and the assertion in the most recent supplement of "no doubt that ondansetron heralds a new era in antiemetic therapy."¹⁵

NEED FOR NEW REGULATORY BODY

Part of the fault lies in the current United Kingdom drug regulations, which have no requirement for relative efficacy. The drug companies are unlikely to want change, and self regulation by the Association of the British Pharmaceutical Industry is not enough.¹⁶ Chalmers and Herxheimer asked who should get involved in trials of drugs.⁷ Once a drug company has shown that a new drug works it should be supported by an agency that, unlike the present Medicines Control Agency, is given government support and mandated powers to run comparative trials. Drugs should not be available to clinicians, certainly not within the NHS, until this information is available. This is the situation in Australia, where reimbursement is made only for prescribed drugs accepted as in some way better than drugs available previously.

Key messages

- Clinicians cannot make decisions about new drugs unless they are tested against other active drugs
- Placebo controlled trials may be unethical if active drugs are available
- Drug regulations should be altered to make comparative data mandatory for licensing
- Drug research should be funded in parallel by the companies and the NHS once drugs are proved safe and effective

The American Food and Drug Administration requires placebo controlled trials. Rothman and Michels reject this requirement when there is already an effective treatment and cite the criticism of the early placebo controlled trials of ondansetron in oncology.¹⁷ We agree. Many investigators defending the placebo controlled trials pointed out that ethics committees gave approval. We find this hard to understand, particularly for the trials of treatment of nausea and vomiting. We wonder what information about current antiemetics the committee was given. Would the members of the committees themselves be happy to receive placebo for postoperative vomiting?

Ondansetron is the first of what will be several 5HT₃ antagonists used for postoperative nausea and vomiting. There are many other groups of drugs in which redundancy is partly due to lack of the need for comparison. Evidence for the effectiveness of antibiotic prophylaxis for caesarean section was strong by the early 1970s, but placebo controlled trials continue.⁷ The government is keen to ensure that money paid under the pharmaceutical price regulation scheme should be "directed towards medically useful research."¹⁸ Trials would have been more useful and had more point if comparator drugs had been used.

One of the first published trials of a newer 5HT₃ antagonist, tropisetron, included a placebo arm but tested droperidol and metoclopramide as well.¹⁹ It is difficult to see why ondansetron could not have been tested in this way from the outset.

We thank Dr Iain Chalmers for helpful comments and suggestions.

Funding: None.

Conflict of interest: None.

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(Accepted 25 July 1995)

Incidence of transfusion associated B and non-A, non-B hepatitis in Italy

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BMJ 1995;311:846-7

Screening of donated blood for hepatitis B surface antigen and for serum alanine aminotransferase concentration has been performed in Italy since the early 1970s. Screening for other surrogate markers, such as antibody to hepatitis B core antigen has never been done. Screening for antibodies to hepatitis C virus was routinely done in a few blood banks since 1990; it became compulsory in 1991. Second generation enzyme linked immunosorbent assay (ELISA) was introduced in 1992 in all blood banks.

Using data from the surveillance system for acute viral hepatitis (SEIEVA), we have evaluated the incidence of transfusion associated B and non-A, non-B hepatitis in Italy from 1987 to 1993.

Methods and results

SEIEVA, which is coordinated by the Istituto Superiore di Sanità in collaboration with health districts, started in 1985.¹ From 1985 to 1993 the number of health districts participating in SEIEVA has greatly increased, in 1992 covering about 40% of the Italian population. SEIEVA uses weekly notification of cases and a standard questionnaire for data collection on risk factors.

Patients with acute hepatitis with hepatitis B surface antigen and IgM antibodies to hepatitis B core antigen, without antibodies to hepatitis A, are classified as having hepatitis B. Those without IgM antibodies to hepatitis B core antigen and without IgM antibodies to hepatitis A are classified as having non-A, non-B hepatitis. Tests for IgM antibodies to hepatitis B core antigen have been available since 1987. Assays of hepatitis markers are performed in different laboratories scattered all over the country. No changes were made in the notification system during the study period.

Using as denominators the catchment populations of the participating health districts, incidence rates per 1 000 000 of notified cases of transfusion associated hepatitis decreased from 1.4 in 1987 to 0.5 in 1992 for hepatitis B and from 4.4 in 1987 to 0.3 in 1992 for

Incidence rates per 1 000 000 of notified cases of hepatitis B and non-A, non-B with history of blood transfusion in Italy 1986-93

Year	Hepatitis B	95% confidence interval	Hepatitis non-A, non-B	95% confidence interval
1987	1.4	(0.7 to 2.1)	4.4	(3.2 to 5.6)
1988	1.4	(0.8 to 2.0)	4.5	(3.5 to 5.6)
1989	1.8	(1.1 to 2.4)	4.1	(3.1 to 5.1)
1990	0.9	(0.5 to 1.4)	2.9	(2.1 to 3.7)
1991	0.8	(0.4 to 1.3)	1.4*	(0.8 to 2.0)
1992	0.5	(0.2 to 0.8)	0.3†	(0.1 to 0.6)
1993	1.0	(0.6 to 1.5)	0.4	(0.2 to 0.7)

*ELISA-I screening introduced by law in all blood banks.

†ELISA-II screening introduced.

ELISA=Enzyme linked immunosorbent assay.

non-A, non-B hepatitis. Although for hepatitis B the incidence increased from 1992 to 1993, the 95% confidence intervals for these periods overlapped. For non-A, non-B hepatitis the low 1992 rate remained virtually unchanged in 1993. Compared with 1989, the incidence of cases of non-A, non-B hepatitis reporting blood transfusion decreased from 4.1 per 1 000 000 in 1989 to 2.9 in 1990 (−29%), when screening with first generation ELISA (ELISA-I) was routinely done in a few blood banks, to 1.4 in 1991 (−66%) when this screening became compulsory, and to 0.3 (−93%) in 1992, after ELISA-II was introduced.

Comment

Our findings show a small residual risk of transfusion associated hepatitis B and indicate the effectiveness of the screening policy for antibodies to hepatitis C virus in reducing the incidence of cases of non-A, non-B hepatitis after blood transfusion.

Because the viral surface antigen may be present in the serum at a low concentration or may be masked in immune complexes, it has been shown² that blood donors testing negative for hepatitis B surface antigen may transmit hepatitis B virus infection.² Transfusion with "HBsAg negative" blood is thus a potential source of infection.

Cohort studies from Japan³ and the USA⁴ have documented decreases of 60 to 80% in the incidence of post-transfusional non-A, non-B hepatitis after the implementation of donor screening for antibodies to hepatitis C virus by ELISA-I in addition to, or at the same time as, screening for surrogate markers. A recent report from Spain has shown that for antibodies to hepatitis C virus testing by ELISA-II further reduces the incidence of non-A, non-B hepatitis by 57% when compared with ELISA-I.⁵ Although information obtained through passive surveillance is likely