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Myths and realities of antiemetic treatment

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One of the areas of supportive care in oncology which has undergone significant changes over the past few years is antiemetic therapy. The recent progress made in this field has been so remarkable that the attitude of the majority of oncologists towards the possibilities of controlling chemotherapy-induced emesis has evolved from one of excessive pessimism to another of generalised and, perhaps unrealistic, optimism. Consequently, several untrue or partially untrue beliefs (myths) about this topic emerged in the past or have recently been put forward (Table I). In the following pages, we will attempt to analyse the veracity of some of these beliefs by carefully reviewing the enormous amount of data on antiemetic therapy which is currently available in the medical literature. The first part of this paper will deal with the old myths and beliefs of the 1970's, an era in which little attention was paid to emetic control. The antiemetic revolution of the 1980's will be analysed next, and the achievements of this intense period of research will be summarised. Lastly, we will discuss the current concepts of antiemetic control which have emerged from the vast experience obtained over the past decade. Since most oncologists tend to be overly optimistic at present, a special emphasis will be placed on the analysis of current questions, unsolved problems and the limitations of antiemetic control.

Chemotherapy-induced emesis: the old myths

During the 1970's, three myths concerning chemotherapy-induced emesis and emetic control were widely extended among oncologists. In the first place, it was commonly believed that chemotherapy-induced emesis was a minor problem of cytotoxic treatment, and, as a result, only 20 antiemetic trials were published during this decade (Penta *et al.*, 1981*a*). Needless to say, this belief was clearly erroneous. In 1980, we took a survey of 156 cancer patients who had received a total of 821 courses of intravenous chemotherapy with several combinations of drugs during the previous 3 years (Martin Jimenez *et al.*, 1988*a*). In accordance with our antiemetic policy at that time, none of these patients had received prophylactic antiemetic treatment. Table II shows the incidence of emesis in this survey. Seventy-nine per cent of the patients vomited at some time during the overall period of treatment. Even if we exclude those patients treated with cisplatin, which was introduced into clinical practice in the late 1970's, 75% of the remaining patients still experienced postchemotherapy vomiting.

During the 1970's and especially in the following decade, a number of reports appeared which also contradicted the idea that emesis was only a minor problem of chemotherapy. Several reports pointed out that antineoplastic chemotherapy-induced nausea and vomiting not only caused severe discomfort to patients, but could also produce physical lesions (Enck, 1977; Martin-Jimenez *et al.*, 1988*b*). More important still, it was reported that vomiting associated with chemotherapy could become a dose-limiting, and even a lethal toxicity in those patients who abandoned curative cytotoxic treatments due to severe emetic symptoms (Laszlo, 1983).

The second myth from the 1970's was based on the assumption that emetic symptoms, like myeolsuppression or alopecia, were an inevitable consequence of chemotherapy and a rather small price to be paid in exchange for the benefits obtained from the treatment. Since this belief was widely extended among oncologists, it is not surprising that only a few isolated voices emphasised the need for research into effective antiemetic treatments. In a letter to the Editor of the *New England Journal of Medicine*, Whitehead pointed out that 'one toxic manifestation of chemotherapy – namely, gastrointestinal toxicity – appears not to have received sufficient criticial attention' and made 'a plea to all co-operative chemotherapeutic groups to undertake a search for effective antiemetic therapy as an additional and integral part of current and future chemotherapeutic trials' (Whitehead, 1975). Unfortunately, this appeal did not arouse much interest in co-operative groups and, therefore, the search for effective antiemetic therapy had to be put off for some years. Another widely accepted myth in the 1970's was that antiemetics were of little or no value in the control of chemotherapy-induced emesis. A survey taken in 1981 in 56 American institutions revealed that only 21.4% of medical oncologists and 15.8% of paediatric oncologists felt conventional antiemetics were beneficial in alleviating cancer chemotherapy-induced nausea and vomiting (Penta *et al.*, 1981*b*). It is important to note that most of the conventional drugs which demonstrated an unquestionable antiemetic efficacy in the next years (such as metoclopramide, corticosteroids, procholoperazine, haloperidol and droperidol) were already available in the 1970's.

In conclusion, the three most extended beliefs about chemotherapy-induced emesis and antiemetic control which were present during the 1970's have been proven to be false in the light of current knowledge acquired in this field.

The 1980's: a decade of progress in emetic control

The clinical introduction of cisplatin constituted the main impulse of the antiemetic revolution which took place in the 1980's. The severe emesis induced by this drug surprised most oncologists, who were unprepared to deal with the problem. The initial contact with the new drug was so dramatic that it stimulated investigators into making an important effort in research, which eventually led to significant advances in emetic control.

The first major step in the control of cisplatin-induced emesis was the introduction of high-dose metoclopramide (Gralla *et al.*, 1981). As an individual agent, high-dose metoclopramide provided complete protection to about one

Table I Myths of chemotherapy-induced emesis and antiemetic therapy

Old myths:	
	– Chemotherapy-induced emesis is a minor problem of therapy
	– The emetic symptoms are an inevitable consequence of treatment.
	– Antiemetics are of little or no value in the control of chemotherapy-induced emesis.
New myths:	
	– The great majority of patients can now obtain a complete control of emesis with the currently available antiemetics.
	– Chemotherapy-induced emesis is no longer an important problem for cancer patients.

Table II Incidence of chemotherapy-induced vomiting in patients without prophylactic antiemetic treatment[a]

Chemotherapy schedule	*No. of patients*	*No. of courses*	*Courses with vomiting*	*Patients with vomiting*
CMF (1)	11	52	15 (29%)	7 (64%)
COP (2)	12	57	27 (47%)	7 (58%)
C-MOPP (3)	12	39	31 (79%)	9 (71%)
CHOP (4)	19	130	91 (70%)	15 (97%)
CAF (5)	27	162	102 (63%)	21 (78%)
DTIC comb.	33	190	183 (96%)	33 (100%)
CISPLATIN comb.	21	86	86 (100%)	21 (100%)
Other comb.	21	105	41 (40%)	13 (62%)
Total	156	821	576 (70%)	123 (79%)

[a]Reproduced from Martin Jimenez M. *et al.*, 1988*a*, with permission of the Editor. (1): oral cyclophosphamide, I.V. methotrexate and 5-fluorouracil. (2): I.V. cyclosphosphamide, vinctristine and prednisone. (3): I.V. cyclophosphamide and vincristine, oral procarbazine and prednisone. (4): I.V. cyclophosphamide, doxorubicin, vinctristine and prednisone. (5): oral cyclophosphamide, I.V. doxorubicin and 5-fluorouracil.

third of cisplatin-treated patients on the day of chemotherapy and, therefore, it became the cornerstone of antiemetic treatment in these cases. When other classical antiemetic drugs were used in high doses they also proved to be more active. Dexamethasone (Aapro *et al.*, 1983), haloperidol (Grunberg *et al.*, 1984), droperidol (Jacobs *et al.*, 1985) and prochlorperazine (Carr *et al.*, 1985) were as efficacious as metoclopramide or only slightly less active in controlling cisplatin-induced emesis.

Subsequent studies demonstrated that various combinations of some of these antiemetic agents, particularly high-dose metoclopramide plus dexamethasone, were able to increase the complete control rate in up to two-thirds of the patients on the day of cisplatin administration (Kris *et al.*, 1985*a*).

During the first half of the 1980's studies addressing emesis induced by non-cisplatin containing combinations were significantly less numerous than those involving cisplatin-treated patients. The results obtained with high-dose metoclopramide or combinations of antidopaminergic agents and corticosteroids in the former population appeared to be as good as those obtained in patients treated with cisplatin (Tyson *et al.*, 1982; Allan *et al.*, 1986).

During the 1980's, 5-hydroxytryptamine (5-HT) was implicated as a mediator of emetogenic stimuli and several potent and highly selective 5-HT_3 receptor antagonists, such as ondansetron, granisetron and others, were tried in patients treated with emetic chemotherapy. These new antiemetics proved to be more efficacious and less toxic than high-dose metoclopramide in the control of emesis induced either by cisplatin or by non-cisplatin containing combinations (Marty *et al.*, 1990*a*; Bonneterre *et al.*, 1990). As individual agents, the 5-HT_3 receptor blockers are able to provide complete protection against acute emesis in 50 to 70% of the patients under emetic chemotherapy (Hesketh *et al.*, 1989; Tabona 1990). These impressive figures demonstrate that the 5-HT_3 antagonists are the best antiemetics available up to now.

The identification of the antiemetic activity of high-dose metoclopramide and high-dose corticosteroids and the preclinical and clinical development of the 5-HT_3 receptor antagonists are only two examples of the progress which was made during the 1980's. A clear improvement in the methodolgy of clinical trials during this period was also evident, and all these advances have provided the basis for the continuing progress being made today in antiemetic research.

New myths of antiemetic therapy

A superficial analysis of recent antiemetic reports might suggest to many readers that current antimetic treatments are active enough to assure an adequate control of emesis in the majority of patients undergoing chemotherapy. The most recent publications have reported complete control of acute emesis in nearly two-thirds of the patients receiving emetic chemotherapy. Consequently, a number of beliefs concerning antiemetic therapy, including the possibility of complete control for the majority of patients and the concept that chemotherapy-induced emesis is no longer a problem, are currently gaining support among oncologists. Unfortunately, we do not consider such optimism justified after a critical analysis of the experimental circumstances in which trials are carried out and the way in which the results are expressed. Our reluctance in accepting this overly optimistic viewpoint is based on:

(1) The extrapolation of results from clinical trials to the general population of chemotherapy-treated patients should not be done without reservations. The great majority of antiemetic studies are restricted to a selective patient population (Marty, 1990*b*). Common exclusion criteria of these trials are previous chemotherapy, concomitant emesis due to other conditions (i.e. hypercalcemia, hyponatremia, uremia, CNS metastases, gastrointestinal disorders, analgesic treatment), Karnofsky index inferior to 70, severe concurrent illness, etc. These exclusion criteria are adequate for methodological purposes, but it is quite possible that they compromise one of the intrinsic finalities of clinical trials, namely the extrapolation of results to the general population. In addition, the characteristics of eligible patients who actually enter the studies are extremely variable. As many of these characteristics are well known, independent prognostic factors of chemotherapy-induced emesis (i.e. sex, age, previous history of alcohol intake, etc.), the results of the trials may be conditioned by factors other than the emetic stimulus and the antiemetic treatment – making it very difficult to compare the results of trials and generalise about their conclusions. For instance, the same antiemetic regimen, including high-dose metoclopramide, dexamethasone and diphenhydramine, gave very different results in two consecutive trials carried out at the same institution in cisplatin treated patients (Pollera *et al.*, 1989). The first patient sample, with a male/female ratio of 2.8, obtained a complete control rate of 81% in contrast with 56% in the second one, in which the male/female ratio was 0.6. This difference, probably related to the patients' gender, approached the threshold of statistical significance ($P = 0.059$). Another point to keep in mind is that most studies are based on the emetogenic potential of a particular agent, e.g. cisplatin or cyclophosphamide, and they pay little attention to other oncurrent cytotoxic agents which are combined with the main emetic stimulus. The addition of such agents may change the pattern of vomiting and also affect the likelihood of emesis. These factors, and others which are frequently overlooked, may be the cause of the contradictory results found in clinical trials. In a classical study, high-dose metoclopramide did significantly better than placebo against vomiting induced by cisplatin in combination

with vindesine, in a population mainly composed of male patients (Gralla *et al.*, 1981). On the other hand, in another trial, the same schedule of metoclopramide did not provide better protection than no antiemetic therapy. In this study the patients, the majority of whom were female, were treated with cisplatin in combination with another emetogenic drug – doxorubicin (Romeling *et al.*, 1985). This study and others have shown that a subset of poor-risk patients, in particular young women treated with high-dose cisplatin in association with doxorubicin/cyclophosphamide, did not actually achieve a good control of vomiting with the most active antiemetic regimens (Pollera *et al.*, 1989; Martin Jimenez *et al.*, 1987; Roila *et al.*, 1989).

(2) The way in which antiemetic results are usually communicated can lead to a distorted interpretation of reality. This has become particularly evident since the introduction of the concept of delayed emesis after cisplatin treatment (Kris *et al.*, 1985*b*). This phenomenon is defined as emesis occurring more than 24 h after the administration of high-dose cisplatin and affects most patients, even when it is possible to control vomiting on the day of chemotherapy. Although the concept of delayed emesis as a distinct emetic syndrome (Kris *et al.*, 1989) is questionable, some support for this theory can be found in the case of cisplatin. This drug produces an intense but short period of emesis, limited to the first 12–24 h after chemotherapy in patients who do no receive concomitant antiemetic prophylaxis (Martin Jimenez *et al.*, 1985). The appearance of nausea and vomiting more than 24 h after cisplatin administration is possibly an iatrogenic phenomenon, due to a rebound effect after an early cessation of antiemetics. Conversely, other cytotoxic agents or combinations, such as high-dose cyclophosphamide, FAC (5-fluorouracil, doxorubicin, cyclophosphamide) chemotherapy or carboplatin, present quite different patterns of emesis, characterised by longer latency periods after the administration of chemotherapy and more prolonged periods of postchemotherapy emesis (Fetting *et al.*, 1982; Martin Jimenez *et al.*, 1988*c*; Martin *et al.*, 1990*a*,*b*). For instance, the majority of patients under FAC chemotherapy (Figure 1) experience vomiting for two or more days. It does not make much sense and it also sounds rather artificial to use the concept 'delayed emesis' in patients treated with cytotoxic drugs that usually induce prolonged periods of emesis. In spite of this incongruity, the majority of recent antiemetic trials describe the results obtained in the first 24 h (acute emesis) separately from those obtained in the four following days (delayed emesis). Expressing results in this way creates difficulties in the interpretation of the real incidence of emesis and can lead to overestimation of the true efficacy of antiemetics. Figure 2 shows a hypothetical example in which the results of a new antiemetic have been analysed in two different ways. Three of the six patients did not vomit during the day of chemotherapy, although two of them did vomit on the following days. The rest of the patients vomited from the first day on. If we express these results in terms of 'acute' versus 'delayed' control, complete (no vomiting) and major (0–2 vomiting) protection against acute emesis was achieved in 50% and 67% of the patients respectively, while a major control against delayed emesis was achieved in 67 to 100% of the patients on days 2 to 5. This way of communicating results, used in many recent trials, suggests that the new antiemetic is very effective in controlling cytotoxic-induced emesis. However, it we report the results over the whole 5 day period (overall analysis), the complete and major protection rates would be 17% (one out of six) and 33%, (two out of six) respectively. The latter way of reporting emetic control apparently leads to worse results, but, in our opinion, it provides a better definition of the real protection achieved by patients.

(3) We lack antiemetic guidelines for a number of cytotoxic treatments, such as intraperitoneal cisplatin and the

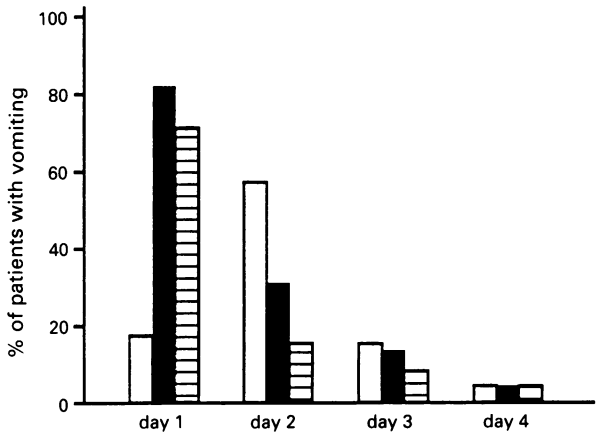

Figure 1 The spontaneous course of FAC-induced emesis. Incidence of vomiting in breast cancer patients ($n = 31$) treated with 5-fluorouracil (500 mg m^{-2} i.v.), doxorubicin (50 mg m^{-2} i.v.) and cyclophosphamide (500 mg m^{-2} i.v.) without anti-emetic prophylaxis; pattern of vomiting over 8 h periods (8 am–4 pm □; 4 pm–12 pm ■; 12 pm–8 am ▤) on the day of chemotherapy (day 1) and the 3 following days (days2–4). Reproduced from Martin Jimenez M *et al.*, 1988*c* with permission of the Editor.

	No. of vomits on day				
pt. no	1*	2	3	4	5
1	0	0	0	0	0
2	0	2	1	0	0
3	0	2	0	0	0
4	2	2	0	0	0
5	7	3	1	0	0
6	8	5	2	1	1

(*) day of chemotherapy treatment

→ ACUTE Vs DELAYED ANALYSIS

CC/MC ACUTE VOMITING: 50%/67%

MC DELAYED VOMITING: 67 TO 100% on days 2 to 5

→ OVERALL ANALYSIS

CC: 17%
MC: 33%

Figure 2 Reporting the results of a new anti-emetic treatment in six patients with the same data analysed in two different ways: acute and delayed emesis data considered separately and together; CC: complete control (no vomiting); MC: major control (0–2 vomiting episodes).

new intensive chemotherapeutic protocols. Vomiting provoked by intraperitoneal cisplatin in ovarian cancer patients is extremely difficult to control for us, in spite of a generous use of high-dose metoclopramide plus corticosteroids. Several variables might be responsible for these poor results: the gender of the patients, the previous use of systemic chemotherapy, the particular pharmacokinetics of cisplatin after intraperitoneal administration and, perhaps, the generation of additional emetic stimuli not strictly related to chemotherapy – namely peritoneal irritation or abdominal distention. Likewise, the new schedules of intensive chemotherapy, now widely used as conditioning therapy for bone marrow transplantation, provoke a severe emesis which cannot be controlled by conventional antiemetics. An anecdotal report on 12 patients treated with high-dose cisplatin (40 mg m^{-2} day^{-1} × 5 days) in combination with high-dose etoposide or high-dose BCNU (on days 2, 3 and 4) has recently been published. The results of this report showed that ondansetron was not sufficient to control vomiting, especially in the period during which BCNU was administered (Lazarus, 1990). The control of emesis induced by these and other similar treatments is an unsolved problem so far and constitutes a new field for clinical investigation.

(4) Most antiemetic trials only report the results obtained in the first course of chemotherapy, but do not provide data on the evolution of patients during the rest of the cytotoxic treatment. Some isolated studies have claimed a maintenance of antiemetic efficacy in subsequent courses of chemotherapy, but a detailed analysis of their results does not support such a conclusion. In one study, where 18 patients were treated with repeated courses of cisplatin, the main conclusion stated that the efficacy of antiemetic prophylaxis with metoclopramide plus dexamethasone was maintained during subsequent courses of therapy (Cognetti *et al.*, 1986). Although 12 out of 18 patients (67%) obtained a complete control in the first course, this control was only maintained in 22 of the 53 subsequent courses of therapy (41.5%). Despite the fact that statistical evaluation did not show any significant differences between the first and the following courses in this study, the power of the analysis to detect real differences was not defined and a clear trend towards worse results in repeated courses of chemotherapy was evident. In another trial, 56 selected patients who experienced two or fewer episodes of emesis during their initial treatment with high-dose cisplatin and ondansetron received the same antiemetic schedule during 132 retreatment courses. (Werner *et al.*, 1989). After a median follow-up of three courses (range 2 to 10), a major control of emesis (two or fewer vomiting episodes) was maintained in 85% of the patients, while 15% did worse in subsequent courses of treatment. Since patients who failed to have good antiemetic control in the first course of chemotherapy were not included in the analysis of data, these figures underestimate the actual loss of efficacy over the time of antiemetic treatment. Two other studies offered further evidence of a loss of antiemetic efficacy in subsequent cycles of chemotherapy. In the first of these studies, where two different schedules of high-dose metoclopramide plus corticosteroids were compared, the protection from cisplatin-induced vomiting suffered a statistically significant decrease in subsequent cycles of treatment. The complete protection rate with the most active of the antiemetic schedules under comparison dropped from 73.4% in the first course to 51.9% in the third course of chemotherapy (Roila *et al.*, 1989). In the second study, the percentage of patients under cisplatin treatment who presented 3 or less emetic episodes with metoclopramide-dexamethasone-diphenhydramine was 93% in the first course. However, the percentage fell to 77.3% in subsequent retreatments after a mean follow-up of three courses (Abad-Esteve *et al.*, 1986).

The majority of the above mentioned studies were not designed to assess the results of antiemetic treatments during the entire period of chemotherapy and the maintenance of antiemetic efficacy was only analysed as an anecdotal part of the overall results. Conversely, one study carried out in our institution was especially designed to describe the evolution of emetic control in 113 breast cancer patients who received six courses of adjuvant FAC chemotherapy and antiemetic prophylaxis with methylprednisolone, thiethylperazine and amitryptiline (Martin *et al.*, 1990). All patients received the same antiemetic treatment during the overall period of chemotherapy in spite of the antiemetic results obtained in the first courses of treatment. At the time of analysis, 81 out of the 113 patients (72%) had completed the expected period of treatment while the remaining 32 patients were still on treatment. Overall, 578 courses of chemotherapy were available for analysis (mean number of courses per patient: 5.1). The major protection rate (0–2 vomiting episodes) decreased in the overall population from 77% in the first course to 62% in the sixth. In the 81 patients who completed the six courses of treatment, the loss of efficacy was quite similar (Figure 3). In the later population, there was a statistically significant difference in the number of vomiting episodes between the first and the last courses of FAC chemotherapy (mean number of 1.9 and 4, respectively, $P = 0.0019$). All these data strongly suggest that there is a moderate but evident loss of efficacy of antiemetic treatments during subsequent courses of chemotherapy. Nearly 15 to 20% of those patients who obtain a major control of emesis during the first course of chemotherapy do not maintain this protection throughout the overall treatment.

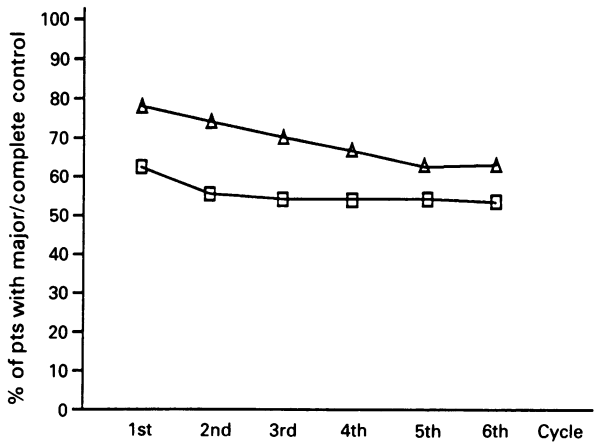

Figure 3 Control of emesis with subsequent treatments; efficacy of anti-emetic treatment (methylprednisolone i.v. + thiethylperazine po + amitryptiline po) in 81 patients who completed six courses of FAC chemotherapy. Percentage of patients with complete (0 vomiting episodes; □———□) or major (0–2 vomiting episodes; Δ———Δ) control of vomiting over the 5 days following chemotherapy.

Conclusions

There can be no doubt that the efforts made in research during the past decade were largely responsible for refuting the old pessimistic myths about chemotherapy-induced emesis. Recent studies have shown that the definitive solution to the problem of emesis is a realistic goal which can be reached in the near future.

Although the new antiemetic treatments have significantly decreased the intensity of emesis in the great majority of patients, their impact on the incidence of emetic symptoms continues to be less than optimal. According to data obtained from medical literature, an estimated 40 to 50% of all chemotherapy-treated patients still experience emesis at some point during the overall period of treatment, despite the use of antiemetics. In addition, there are some specific problems of emesis which are currently lacking adequate solutions.

It is therefore, of the utmost importance that research efforts aimed at improving the current status of antiemetic therapy are maintained until the complete control of emetic symptoms becomes a reality for all patients.

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Discussion of Dr Martin's paper

Morrow: Duration of symptoms is a very important factor in assessing nausea. If we look at the effect of anti-emetics and assess nausea and emesis in terms of frequency, severity and duration, then duration seems to change less than any other parameter. Yet, patients report that duration is the single most distressing factor. If a housewife is not functioning for two, three or four days after treatment, this has a far greater impact on her life and a greater bearing on her ability to comply with treatment than a brief, albeit horrific, episode, that is over quickly.

Smyth: Dr Martin made the important point that published reports seem to draw different conclusions when addressing the same question. This is not a shortcoming of the data, but due more to a lack of critical facilities in assessing the data. So many end points and methods are used that we must always be aware of, and critically evaluate, study design.