# A succesful combination in chemotherapy-induced side effects

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Tne *primary toxicities of chemotherapeutic agents are nasuea, vomiting, hypersensitivity reactions and problems related to these symptoms. Various drugs have been used to overcome these symptoms but controversies exist on the dosage, timing and ideal combinations of different drugs. A combination of metoclopramide 1 mg/kg/dose, diphenhydramine 3 mg/kg/dose and dexamethasone 0.5 mg/kg/dose (MDD) was administered prior to 15 minutes and after 1.5 hours of 67 chemotherapeutics interventions in 39 hemato-oncological patient, 29 of whom had leukemia. Placebo was administered in 14 cases. MDD combination was successful in 65.7% of cases whereas the success rate of placebo was only 35.8%. Sixty-nine of cases were sedated. The most successful results obtained by MDD were during the administration of intravenous immunoglobulin (100%), adriamycin-daunomycin (71.4%) and cis platinium (3/4). MDD is an effecitve, safe, easy to use and protective combination for the prevention of chemotherapy-induced side effects in childhood cancers. [Turk J Med Res 1992; 10(5):259-263]*

**Key Words:** Chemotherapy-induced side effects, Metochlopramide, Diphenhydramine, Dexamethasone

Recent developments in chemotherapy have lead to better cure rates in childhood hemato-oncological diseases but have brought along the problem of drug toxicity. The main toxicities of chemotherapeutics include nasuea, vomiting, hypersensitivity reaction and related metabolic disturbances, on the other hand, laceration of the eusophagus, malnutrition, pathological fractures and refusal of the further therapy by the patient are important also (1-4). Hypersensitivity reactions usually consisit of respiratory distress, bronchospasm, hypo or hypertension, anxiety and cutaneus lesion (5-7). Negative psychological reaction towards long-used chemotherapeutics worsen the clinical presentation **(8,9).** The factors associated with the onset, severity and response to therapy of the toxic effects of chemotherapeutics include age, sex, primary disease, clinical status, the route of administration and the single or combined use of chemotherapeutic agents (3,10).

The side effects of chemotherapeutics differ in that they affect different neuro-anotomic areas (4,11-13). For this reason, drugs such as metochlopramide.scopolamine, dexamethasone, haloperidol, cannobinoids, secobarbital and phenothiazines can all be used either as single or combined agents to overcome nausea-vomiting and hypersensitivity reaction (14-16). Recently, a new selective 5HT3 (5 Hydroxytritryptamine) ondansetron has been used succesfully as a single drug in chemotherapy-induced emesis (17,18). The combined therapy has been preferred lately but there is not a consensus yet on the ideal combinations, doses and routes of administration.

We have investigated the efficacy of metoclopramide, diphenhydramine and dexamethasone combination in the treatment of side effects of cytostatic, i'mmunosuppresive and antibiotic therapy of various hemato-onclogic patients.

## MATERIALS AND METHODS

The subjects of this study were 39 hemato-oncological patients treated between November 1990 February 1991 at the Pediatric Hematology-Oncology Department and Our Children Leukemia Foundation Healt Center, İstanbul Medical Faculty. Four patients were treated as out-patients, while the remaining 35 were in-patients. There were 25 boys and 14 girls with a mean age of 7.5±3.5 (range :2-15 years). They were all receiving various cytostatics, immunosuppresive agents and antibiotics. The general characteristic of the cases and the chemotherapeutics they receive are depicted in Table 1.

**Geliş Tarihi:** 10.7.1992 **Kabul Tarihi:** 8.9.1992

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**Table 1.** Study and control groups

| | Study Group n(a) | Control group n(a) | Total n(a) |
|---|---|---|---|
| n | 30 (67) | 9(14) | 39 (81) |
| M/F | 19/11 | 6/3 | 25/14 |
| Age | 7.6(2-15) | 7.5(4-14) | 7.5(2-15) |
| Leukemia | 22 | 7 | 29 |
| Lymphoma | 2 | — | 2 |
| Solid tumors | 4 | 2 | 6 |
| AHA/ITP | 2 | | 2 |
| CTX-IFS | 19 | 8 | 27 |
| ARA-C | 13 | 3 | 16 |
| ADR-DAU | 14 | 3 | 14 |
| IVIG | 10 | | 10 |
| CPDD | 4 | 3 | 7 |
| Act.D | 4 | — | 4 |
| Ampho.B | 3 | — | 3 |

AHA: Autoimmune hemolytic anemia, ITP: Idiopathic thrombocytopenic purpura. CTX: Cyclophosphamide, IFS: Iphosphamide, ARA.C; Cytarabine, ADR: Adriamycin, DAU: Daunomycin, IVIG: Intravenous immunoglobulin, CPDD: Cis-platinum, Act.D: Dactinomycin, Ampho B; Amphotericin B. n: number of cases, a: number of administration, M: Male, F: Female

Thirty patients received prophylactic therapy in 67 courses chemotherapy while 14 courses of chemotherapy in the remaining 9 patients were evaluated as controls. All drug administration were performed at the clinical and kept a diary afterwards at home. Vital signs of in-patients were followed by nurses and physicians.

Patients who had not received any antiemetics, antihistamines or antiallergics, 10-12 hours prior to therapy were enrolled to the study. They did not eat *or* drink anything for the first 6 hours after the there and they were maintained solely on intravenous flui r. Metoclopramide (1 mg/kg/dose), dexamethasone (0.5 mg/kg/dose) and diphenydramine (3 mg/kg/dose) in 50 ml of normal saline were administered 15 minutes before and 1.5 hours after the administration of chemotherapy. Nasuea, vomiting, headache, sedation and other effects (such as number of defecations and extrapyramidal signs) were noted 15 minutes prior and 1/4, 1/2, 1, 1 1/2, 2, 3, 4 hours and 1 day after therapy.

In the control patients, only 50 ml of normal saline were perfused for 15 minutes before and 1.5 hours after the therapy. They did not receive any antiemetics antiallergics or antihistamines in the first 6 hours of therapy but appriopiate therapy was given to patients with severe side effects. However, no patients was excluded from the study for severe side effects.

## RESULTS

### Effectiveness of MDD combination (Table 2)

Metoclopramide (M), diphenhydramine (D) and dexamethasone (D) combination was used in 67 che-

**Table2.** Results

| | Successful Study/Control Group | | Unsuccessful Study/Control Group | | Total Study/Control Group | |
|---|---|---|---|---|---|---|
| Number | 15 | 3 | 15 | 6 | 30 | 9 |
| Leukemia | 12 | 3 | 10 | 4 | 22 | 7 |
| Lymphoma | | — | 2 | — | 2 | — |
| Solid tm. | 1 | — | 3 | 2 | 4 | 2 |
| AHA/ITP | 2 | — | —23 | — | 2 | — |
| Administ. | 44 | 5 | 23 | 9 | 67 | 14 |
| CTX-IFS | 9 | 1 | 10 | 7 | 19 | 8 |
| ADR-DAU | 10 | | 4 | — | 14 | — |
| ARA-C | 7 | 3 | 6 | — | 13 | 3 |
| IVIG | 10 | | | — | 10 | |
| CPDD | 3 | 1 | 1 | 2 | 4 | 3 |
| Act. D | 4 | | — | — | 4 | — |
| Ampho.B | | | 2 | | 3 | — |
| % | 65.7 | 35.8 | 34.3 | 64.2 | 100 | 100 |
| M/F | 9/6 | 3/0 | 10/5 | 3/3 | 19/11 | 6/3 |

AHA: Autoimmune hemolytic anemia, ITP: Idiopathic thrombocytopenic purpura. CTX: Cyclophosphamide, IFS: Iphosphamide, ARA.C; Cytarabine, ADR: Adriamycin, DAU: Daunomycin, IVIG: Intravenous immunoglobulin, CPDD: Cis-platinum, Act.D: Dactinomycin, Ampho B; Amphotericin B. n: number of cases, a: number of administration, M: Male, F: Female

motherapy administration in 30 patients. In 15 patients (50%) and 43 administration (67.5%) MDD combination was succesful and no side effects were noted. It was ineffective in the remaining 15 patients and 24 administration (34.5%). MDD was effective in 10 of 14 adriamycin-daunomycin administration (74.4%), in all of 10 intravenous immunoglobulin (100%), and in 3 of 4 cis-platinum administrations. Succès rates were 53.8 per cent for cytarabine, and 47.3 percent for cyclophosphamide-ifosphamide administrations.

MDD effectiveness according to the primary disease could not be evaluated because of nonhomogenous distribution. MDD was effective in 9 of 19 boys (47.3%) and 6 of 11 girls (54.5%). As for age, it was effective in 4 of 18 patients between 0-15 years, 9 of 15 patients between 6-11 years, and 2 of 5 patients older than 11 years.

## Control group

Nine patients received placebo in 14 administration of chemotharepy and the effects of psychological factors were assesed. In 3 cytarabine, 1 cyclophosphamide and 1 cis-platinum administration, placebo were succesful 5 cases (35.8%). In the unsuccesful cases, 7 cyclophosphamide, and 2 cisplatinum administrations had performed. Three of 6 boys and all of 3 girls were in the unsuccesful group.

## Toxicity

Of 67 administrations, sedation, sweating and irritation were seen in 46 (68%) cases. Sedation and sweating were noted in 24 administrations (35.8%), only sedation was noted in 19 administrations (20.3%), only sedation and only irritation were seen in 1 administration each. In the control group, fatigue, sense of coldness and sedation were seen after 4 administration (28.5%).

## DISCUSSION

It is a well-known that chemotherapeutics used in the treatment of hemoto-oncological diseases may induce severe life-threathening reactions. The majority of these reactions are nasuea, vomiting and allergic eruptions.Respiratory distress, bronchospasm, anaphlaxis, hypotension and hypertension, nasuea, vomiting, fever headache and allergic skin reactions lead to organic and psyhcological disturbances (3,5,6).

Unpleasesant side effects differ according to the primary disease and the chemotherapy agents used. All agents, but especially cis-platinium, cyclophosphamide and cytarabine induce nasuea and vomiting. Nasuea and vomiting should be treated promptly and systemically because It may lead to metabolic turmoil along with eusophagial laceration, malnutration and refusal of further therapy by the patient (1,7,10,14).

Cis-platinium induces hypersensitivity reactions in 20% of cases and it may even be fatal in 5% of them. On the other hand, antitumor antibiotics such as adriamycin, bleomycin and dactinomycin may cause febrile reactions, respiratory distress, sedation and hypotension (5,6). Epipotophyllins may induce all kinds of allergic reactions although mild. Recently intravenous immunoglobulins (IVIG), vancomycin and amphotericin-B have been used extensively and they have also similar side-effects. Since all chemotherapeutics have more or less side effects, they should be used only in the clinic, under the supervision of doctors and if any, after the test doses have been given. All vital signs of the patients should be monitored before and during the use of the agent and since most of side effects develop within the first 15 minutes after the administration of the agent, the patient should be kept under close surveillance.

Various drugs such as phenothiazins, metochlopramide, scopolamine, haloperidol, lorazepam, tetrahydrocannabiol, secobarbital, chlorpromasine and dexamethasone and ondonsetron have been used to overcome the side effects of chemotherapeutics both in children and in adults (9,13,17). Chemotherapy agents have different modes of actions, hence different side effects. For that reason combination of these drugs have been widely used (15,16,18).

There is no consensus of opinion yet on the doses, intervals and route of administration of these combination (15,16). Metoclopromide was initally used to prevent radiaton-induced emesis; but later it was also used to overcome the side effects of chemotherapeutics also, metoclopramide blocks dopamine in central nervous system and suppress chemoreceptor trigger zone: but it leads to extrapyramidal reactions and diarrhea by increasing gastrointestinal motility, these effects are more common in children (9,11,12). To nullify such side effects of metoclopromide and to exploit the antiemetic and antiallergic effects diphenhydramine and dexamethasone have been combined to metoclopromide.

MDD combination was first used by Kris et al. (15) in adult patient to overcome the adverse effects of chemotherapeutics. We used the same regimen with adjusted doses for children. To maintain high plasma concentrations, it was 65.7% succesful in our study. Using a similar regimen, Kris et al reported 55-60%, Richards et al (13) 72% and Marshall et al. (16) 77% success rates.

Dexmethasone has a long half-life; therefore at the second administration, only MD can be considered enough. Kris et al. (15) suggest that only one administration of dexamethasone might be sufficient.

Some authors report that chemotherapy induced nasuea-vomiting and other reactions ore more common in adolescents and in girls but still some authors refuse this observation (10). In bur study group, patients older than 11 years were only a minority and therefore no results could be derived. Large samples

are needed for this purpose. There were no differences between sexes.

Cis-platinium, cyclophosphamide, metochlorethamine and adriamycin are the most notorius chemotherapeutic agents for nausea and vomiting. Allergic rections are more common with the use of cis-platinium, etoposite, adriamycin bleomcycin, and amphotericin B. Anideal anti-emetic and anti allergic combination, therefore, should be sufficient enough to prevent such complications (8,18).

In our study, the most succesful effect was seen after the administration of IVIG. There were no side effects in all of 10 IVIG administered patients. Success was 71.4% in 14 adriamycin-daunamycin given patients and 53.8% in 13 cytarabine given patient. MDD was quite successful in 3 patients given cis-platinium and in all of 4 patients given dastinamycin, placebo was perfused during 8 cyclophosphamide and 3 cis-platinium administrations and reactions were not seen in only 1 case. Therefore, it is obvious that MDD was successful in preventing adverse reactions of chemotherapeutics.

Terrin et al. (2) could prevent emesis by metoclopramide and diphenhydramine in 50-55% cases. Marshall et al. (16) were successful by chlorpromasine in 19% with metoclopramide, dexamethasone and scopolamine whereas Richard et al. (13). Side effects of drugs to overcome the adverse effects of chemotherapeutics have limited their single use. With combined therapy most of the major adverse effects are eliminated but sedation, sweating and diarrhea can be seen. Richard et al. and Marshall et al. underline sedation as part of the antiemetic effect (13,16). Marshall et al. have found the same rate for antiemetic and sedation effects.

In our study, the success rate was 65.7% and sedation was seen 68.5% of cases. However sedation was observed in 28.5% of the placebo group and this suggests that such effect connot be solely attributed to MDD but the performance scale and prior activity of the child may play an important role also.

The experience gained throught the previous administration of chemotherapy agents might play an important role in the presentation of side effects. Psychological support is indispensible to all combinations. Placebo was used in 14 chemotherapy agents administrations and no side effects were seen in 35.8% of them. In 23 cases, who had shown severe reactions with prior administration of chemotherapeutics MDD was successful in 56.5% of them. This, also shows the efficacy of the combinations.

As a result, MDD combination is an effective, safe and easy regimen to overcome the metabolic, traumatic and psychological problems faced by the child receiving chemotherapeutics for cancer.

**Kemoterapi ajanlarının başlıca toksik etkileri**

*Kemoterapi ajanlarının başlıca toksik etkileri bulantı, kusma, hipersensitivite reaksiyonları ve bunlara ilişkin problemlerdir. Bu semptomlara yönelik olarak değişik ilaçlar kullanılmış fakat dozaj, zamanlama ve ideal kombinasyonlar konusunda bir görüş birliği yoktur. Yirmidokuzu lösemili 39 hemato-onkoloji hastasında metoclopramide, 1 mg/kg, diphenhydramine 3 mg/kg ve dexamethasone 0.5 ml/kg (MDD) kombinasyonu 67 kemoterapi uygulamasından 15 dakika önce ve 1.5 saat sonra olmak üzere uygulandı. 14 vakaya plasebo verildi. MDD kombinasyonu hastaların %65.7'sinde başarılı iken plasebo ancak %35.8'inde başarılı oldu. MDD ile en başarılı sonuçlar intravenöz immunoglobulin (%100), adriamycindaunomycin (%71.4) ve cis-platin (3/4) uygulamaları esnasında elde edildi. MDD, çocukluk çağı kanserlerinde kemoterapiye bağlı yan etkilerin önlenmesinde etkili, güvenilir, kullanımı kolay bir kombinasyondur. [Türk Tıp Araştırma 1992; 10(5):259-263]*

**Anahtar Kelimeler:** Kemoterapiye bağlı yan etkiler, Metoclopramide, Diphenhydramine, Dexamethasone

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