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## Original Paper

# Effects of Intrapleural Mitoxantrone and Mepacrine on Malignant Pleural Effusion—A Randomised Study

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**30 patients with malignant pleuritis were randomised to be treated, either with intrapleural instillation of mepacrine chloride or with mitoxantrone. The patients were evaluated with chest X-ray and a symptom questionnaire during a follow-up period of 12 weeks. Mitoxantrone levels in the pleural space and plasma were measured at different time points in some of the patients. High concentrations of mitoxantrone were found in the pleural fluid while the plasma concentrations were low, giving a plasma/intracavity ratio generally of less than 1:60. The chest X-rays showed excellent results for both treatment modalities. However, the patients treated with mepacrine chloride experienced greater discomfort with fever and pain, and those treated with mitoxantrone reported significantly less dyspnoea and less asthenia after 4 weeks. We conclude that both treatments are equally effective in preventing the recurrence of malignant effusion. However, mitoxantrone seems to have further advantages when it comes to improving the quality of life.**

**Key words: malignant pleuritis, mitoxantrone, mepacrine, pleural effusion**
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## INTRODUCTION

EARLY TREATMENT of malignant pleural effusion reduces patient discomfort and appears to prolong survival [1]. Chemical pleurodesis using tetracycline [2, 3] and mepacrine chloride [4] are well-documented treatment methods. A response rate of 85–90% is generally expected. However, patients usually suffer from fever and pleuritic pain, and suction treatment is often needed in order to guarantee an optimal response.

Nitrogen mustard was the first cytotoxic drug used in the treatment of malignant pleural effusion [5–7]. Subsequently a variety of drugs used singly or in combination have been tried with various results including thiothepa [4], etoposide [8], mitomycin [9], cis-platinum [10] and doxorubicin [11, 12]. Bleomycin has been frequently used since it has both sclerosing and cytotoxic properties [13–16]. It is still not clear whether bleomycin with its dual properties is superior to sclerosing treatment alone. One major drawback with locally administered cytotoxic agents is the rapid absorption from the pleural cavity to the systemic circulation. It is thus difficult to achieve high enough intrapleural concentrations without systemic toxicity. Intrapleural administration of the anthracyclines, doxorubicin and mitoxantrone, result in high pleural concentrations and low risk of systemic side-effects [17, 18]. Mitoxantrone has the additional advantage of being less toxic to normal tissue with accidental extravascular administration. It has been reported to be effective in the treatment of malignant pleural effusion [19]. The aims of the present study were to evaluate whether locally administered mitoxantrone was as effective as mepacrine chloride in preventing recurrence of pleural effusion. Another aim was to compare how these two treatment modalities influenced the well-being of the patient, during and after the treatment period. Furthermore, we wanted to assess the pharmacokinetics of intrapleural mitoxantrone administration.

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## PATIENTS AND METHODS

Patient characteristics are shown in Table 1. 30 patients (4 males, 26 females, mean age 62 years, range 42–82 years) were included. Criteria for inclusion were: malignant pleural effusion verified by cytology, an expected survival time of more than 3 months (Karnofsky index $> 60$), no concomitant cytotoxic treatment within 1 month prior to inclusion and a verified symptomatic progression of pleural effusion within the last month. The patients were then randomised to treatment either with mitoxantrone or mepacrine chloride. 2 patients suffered

*Table 1. Patient characteristic data. 30 patients were initially included. 2 patients were excluded. 1 patient in the mitoxantrone group died unexpectedly of pulmonary embolism before initiation of the treatment. 1 patient in the mepacrine group suffered from a stroke just before initiation of the treatment. ">" means that the patients were still alive at the last follow-up.*

| | Age | Sex | Tumour origin | Survival (months) | Comments |
|---|---|---|---|---|---|
| Mepacrine | | | | | |
| Patient | | | | | |
| 1 | 82 | F | Lung | 5 | |
| 2 | 70 | M | Lung | 9 | |
| 3 | 56 | F | Ovary | 6 | |
| 4 | 65 | F | Lung | 4 | |
| 5 | 71 | F | Breast | 1 | |
| 6 | 65 | F | Breast | 4 | |
| 7 | 68 | F | Ovary | 9 | |
| 8 | 73 | M | Lung | 7 | |
| 9 | 50 | F | Breast | 3 | |
| 10 | 68 | F | Ovary | 7 | |
| 11 | 54 | F | Breast | >20 | Lung metastasis, no effusion |
| 12 | 74 | F | Breast | 18 | |
| 13 | 58 | M | Lymphoma | 3 | |
| 14 | 56 | F | Ovary | >24 | No relapse |
| 15 | 63 | F | Breast | 0 | Early unexpected death* |
| Mitoxantrone | | | | | |
| Patient | | | | | |
| 1 | 73 | F | Lung | 2 | |
| 2 | 59 | F | Ovary | 4 | |
| 3 | 46 | F | Ovary | 4 | |
| 4 | 45 | F | Ovary | 6 | |
| 5 | 43 | F | Lung | 13 | |
| 6 | 75 | F | Ovary | 8 | |
| 7 | 73 | F | Lymphoma | 3 | |
| 8 | 45 | F | Breast | >18 | Stable disease, no effusion |
| 9 | 66 | F | Breast | 4 | |
| 10 | 42 | F | Breast | 6 | |
| 11 | 65 | F | Breast | >18 | No relapse, excellent condition |
| 12 | 63 | F | Breast | 5 | |
| 13 | 46 | F | Ovary | 10 | |
| 14 | 76 | M | Lung | 0 | Early unexpected death* |
| 15 | 70 | F | Ovary | >28 | No relapse |

* Unexpected death after randomisation, before start of treatment.

from unexpected medical emergencies before the initiation of treatment, 1 from each group. Thus, 28 patients were evaluable.

For ethical and practical reasons, it was not possible to blind the study for the involved personnel (mepacrine = yellow, mitoxantrone = blue). The patients were informed that they were going to be treated with either of two treatment modalities but did not know which of them they would receive. Informed consent was given by all patients, and the study was approved by the local ethical committee.

Statistical comparison between the groups was made using Wilcoxon's non-parametric rank sum test for unpaired samples and the Chi-square test. A $P$-value $< 0.05$ was considered to be significant.

*Mitoxantrone treatment*

A standard chest tube Ch12-14 was inserted into the pleural cavity from the anterior axillary line with the tip located posteriorly–caudally. One litre of pleural fluid was initially removed and the pleural space was then emptied by gravity drainage at a maximum rate of 1 500 ml/day. Mitoxantrone, 30 mg diluted in 50 ml 0.9% NaCl, was instilled via the chest drain, which was then closed with a heparin lock (3 ml heparin sulphate, 100 iu/ml). During the first 2 h, the patient was placed in different positions in order to achieve maximum contact between the drug and the pleura. After 48 h, the chest drain was reopened and removed after the pleura cavity was emptied.

*Mepacrine treatment*

Drainage was performed as described above. Mepacrine chloride, 200 mg diluted in 20 ml saline, was instilled intrapleurally and the drain was closed. The patient was then turned for 2 h as above. The drain was then reopened with gravity drainage. On the second day, this procedure was repeated after a second dose of 200 mg mepacrine chloride intrapleurally. If the fluid level on a lateral decubitus chest X-ray exceeded 0.5 cm on any occasion following mepacrine instillation, suction therapy was used. The chest drain was removed when the daily fluid production was below 150 ml.

*Sampling of plasma and effusions*

Pharmacokinetic studies of mitoxantrone were performed in 8 patients. Venous blood samples and samples of effusion (if obtainable) were collected in heparinised glass tubes before mitoxantrone instillation and at time intervals beginning at 10 min and up to 48 h after instillation. A complete blood sample series was obtained in 7 of the 8 patients. In 1 patient, repeated samples from pleura were achieved at the same time as blood samples were taken (Figure 1). Pleura fluid samples were collected from additional patients (one after 24, 48 and 93 h, one after 4 h and one after 72 h) and were immediately chilled with ice. An antioxidant, sodium metabisulphite to a final concentration of 0.001%, was added to the samples which were then stored at −20°C.

*High-performance liquid chromatography of mitoxantrone*

The chromatographic method used was modified from that described by Larson and co-workers [20]. One microgramme of bisantrene (Cyanamid International, Lederle Laboratories, New Jersey, U.S.A.) was added as an internal standard to 1 ml of the sample, and the pH was adjusted to 9.0 with 2 M ammonium sulphate, pH 10. Mitoxantrone and bisantrene were extracted with 5 ml methylene chloride by shaking for 15 min in room temperature. The organic phase was evaporated to dryness under nitrogen and dissolved in 200 μl of mobile phase. 150 μl of the samples were injected by Wisp 710B auto injector (Waters Assoc. Massachusetts, U.S.A.) on a reverse phase Lichrosorb C18 column (4 mm ID × 25 cm, 5 μm, E. Merck, Darmstadt, Germany) preceded by a Bond pack C18 guard column (Waters Assoc.). The column was eluted with acetonitrile and 100 mM sodium formate, pH 3.0 (1:5 by volume) with a flow rate of 1.3 ml/min delivered by a M45 pump (Waters Assoc.). Mitoxantrone and bisantrene were quantified by absorbance at 66 nm with a spectromonitor 3100 (Milton Roy, Florida, U.S.A.) and the signal was integrated by a Macintosh computer (ChroMac 354). The retention times were 7.5 and 12.5 min for mitoxantrone and bisantrene, respectively.

*Pharmacokinetic calculations*

The area under the plasma concentration–time curves (AUC) was calculated from pharmacokinetic modelling [21, 22]. The degree of systemic availability of mitoxantrone after intrapleural administration was calculated according to the principles of Lönnkvist and coworkers [22, 23].

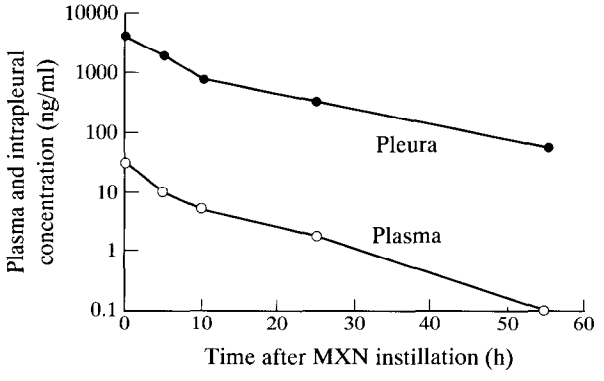


**Figure 1. Plasma and pleura fluid concentrations of mitoxantrone (MXN) measured at different time intervals (h) in 1 patient after instillation.**

*Evaluation of systemic toxicity*

Blood samples were taken before treatment, day 1 and 2, and 1 and 2 weeks after treatment, respectively. Haematological and hepatic toxicity were evaluated according to the WHO's recommendation for classification of acute and subacute toxicity.

*Fever score*

Morning and evening temperatures were recorded during the first 5 days after the initiation of treatment. The fever score each day was recorded according to the WHO's criteria (0 = no fever, 1 = < 38°C, 2 = 38–40°C and 3 = > 40°C). The total fever score for the period was calculated by the formula: Total fever score = Σ day score × numbers of days. (For example, 3 days with fever score 2 + 1 day with fever score 1, total fever score = 3 × 2 + 1 × 1 = 7.)

*Pain score*

A pain score was calculated according to the same principle as for the fever score above. The recorded need for analgesics was graded according to the WHO's recommendation with (0 = no pain, 1 = pain but with no need for analgesics, 2 = pain easily controlled by NSAID (non-steroidal anti-inflammatory drugs), 3 = pain basically controlled by NSAID but with occasional need for opiates, 4 = strong pain with frequent needs for opiate drugs).

*Chest X-ray evaluation*

A chest X-ray evaluation of response (frontal projection + lateral decubitus view) was performed after 4 and 12 weeks, respectively. Comparisons were made with the baseline chest X-ray taken after removal of the drainage tube. The response was graded as: CR = complete response, PR = partial response and PD = progressive disease. A patient with recurrence of pleural fluid, where a new thoracocentesis was not considered to be indicated, was graded as a partial response. The radiological evaluation was made blind by an independent radiologist.

*Symptom questionnaire*

The patients were asked to fill in a simplified symptom questionnaire before treatment, 2 days, 1 week and 4 weeks after treatment. Key questions were "Do you have pain?", "Do you feel short of breath?", "Do you have nausea?", and "Are you tired?". The patients were asked to grade their symptoms on a 10 point scale from "very much (10)" to "not at all (0)". Data are missing from 1 patient in the mitoxantrone group (missing follow-up due to unpredicted social circumstances). The data were collected by a nurse and the first interview was made before or without knowing the randomisation results.

## RESULTS

*Pharmacokinetic studies*

The peak plasma concentrations of mitoxantrone appeared between 10 and 30 min after injection, and the levels varied largely between the patients (median 29 ng/ml, range 7–132 ng/ml). At all times, the intrapleural concentrations were at least 60 times higher than those in plasma (Figure 1) and well above the levels of mitoxantrone reported to be cytotoxic to tumour cells in experimental systems [24]. The $AUC_{0-24\ h}$ of mitoxantrone in plasma varied between 102 and 620 ng/ml h (median 187) corresponding to a systemic availability of 32.3% (95% CI 19.4–55.6%) as compared to mitoxantrone given to patients with acute leukaemia [22].

*Evaluation of drug toxicity*

Haematological toxicity was not observed except in 1 patient in the mitoxantrone group. This patient had grade I leucopenia ($3.4 \times 10^9$/l) at 10 days after instillation, but had previously been treated with cytotoxic regimes and had a leucocyte count just below the lower limit of normal at the start of the treatment. 4 patients in the mepacrine group had signs of liver toxicity with elevated liver enzymes; 3 patients had WHO grade II and 1 had grade I toxicity. Maximum values of liver enzymes were seen 1–2 days after the start of treatment. In all cases, these were normalised at follow up 1 week later. There were no signs of hepatotoxicity in the mitoxantrone group.

*Suction treatment*

10 of the 14 patients in the mepacrine group had a fluid level on the decubitus chest X-ray exceeding 0.5 cm and therefore received suction treatment. In the mitoxantrone group, complete emptying of the pleura was thought to be less crucial, and consequently only 1 patient in this group received suction treatment. The mean number of days with a chest drain for the mepacrine and mitoxantrone groups were 5.9 and 5.1 days, respectively ($P > 0.05$).

*Chest radiography (Table 2)*

Evaluation was made at 4 weeks by a radiologist who was blind of the treatment protocol. In the mepacrine group of 14 patients, there were 11 who had a complete response (CR), 1 with a partial response (PR) and 2 with progressive disease (PD). The corresponding figures in the mitoxantrone group were eleven patients with CR, two with PR and one with PD ($P > 0.05$). The response at 12 weeks was maintained in both groups, with 2 deaths occurring in the mepacrine group ($P > 0.05$).

*Pain and fever scores (Figure 2)*

In the mepacrine group fever was common, but the body temperature rarely exceeded 39°C and lasted for 1–2 days after installation. Fever in the mitoxantrone group was seldom, and never more than 38°C ($P < 0.001$). Pain scores were significantly higher in the mepacrine group ($P < 0.001$), and these patients required more analgesics than the mitoxantrone treated patients.

*Quality of life*

In both groups, there were very few patients who complained of nausea. The most interesting differences found were for the degree of dyspnoea and asthenia at 4 weeks as shown in Figure 3. Mitoxantrone patients reported significantly larger reduction of both symptoms and this improvement was significantly better than for the mepacrine group ($P < 0.001$).

*Table 2. Chest X-ray evaluation, after 4 and 12 weeks of treatment*

| | Mepacrine ($n$ = 14) | | Mitoxantrone ($n$ = 14) | |
|---|---|---|---|---|
| Response | 4 weeks | 12 weeks | 4 weeks | 12 weeks |
| CR | 11 | 10 | 11 | 9 |
| PR | 1 | 2 | 2 | 2 |
| PD | 2 | 0 | 1 | 3 |
| Death | 0 | 2 | 0 | 0 |

CR, complete response; PR, partial response; PD, progressive disease. Recurrence of pleural fluid, not to the extent that a new thoracocentesis was required, was recorded as a partial response.

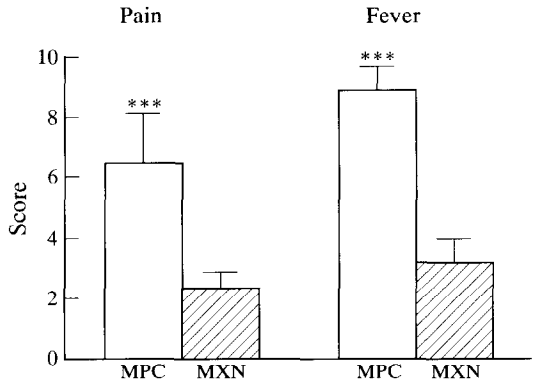


**Figure 2. Pain and fever scores in the mepacrine (MPC) and in the mitoxantrone (MXN) groups, calculated according to the description in the Patients and Methods section. Statistical comparisons between the groups were made with Wilcoxon's non-parametric rank sum test for unpaired samples. *** $P < 0.001$.**

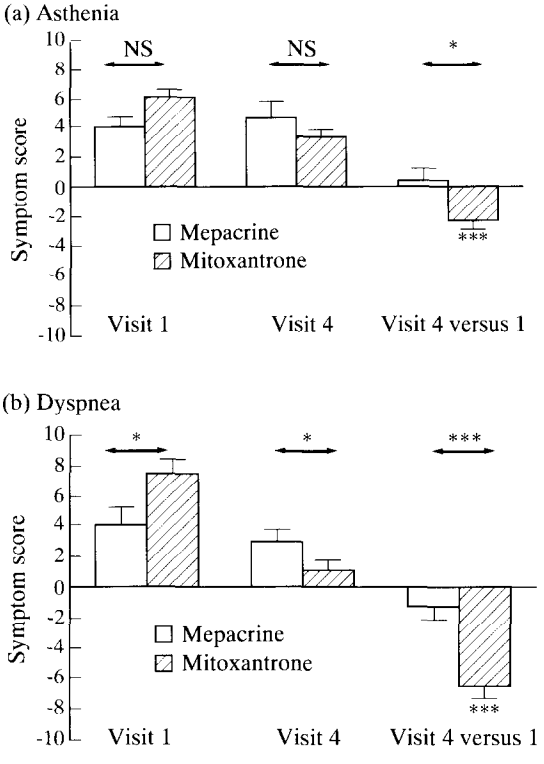


**Figure 3. The patients were asked to score themselves on a 10-graded scale (0 = "not at all", 10 = "very much") if (a) they felt abnormally tired (asthenia) or (b) dyspnoea. The situation after a 4-week follow-up period was compared with their answers before treatment (visit 1). Statistical comparisons between the groups were made with Wilcoxon's non-parametric rank sum test for unpaired samples. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$.**

*Median survival time*

In the mepacrine group this was 6.0 months, compared with 5.5 months in the mitoxantrone group ($P > 0.05$). After a follow-up period of more than 18 months, 5 patients are still alive, 2 in the mepacrine group and 3 in the mitoxantrone group. One patient (breast cancer) has radiological lung metastases without recurrence of effusion. The other patient in the same group (ovary cancer) is still free from relapse 24 months after treatment. 2 patients in the mitoxantrone group (1 breast, 1

ovary cancer) display no signs of recurrence at check up 18 and 28 months after treatment. The third patient (breast cancer) is currently being treated with cytotostatics, and is regarded as a stable disease. None of the patients mentioned above have recurrence of pleural effusion.

## DISCUSSION

The results of the pharmacokinetic study show that high intrapleural concentrations of mitoxantrone are maintained for at least 48 h. The systemic availability of the drug varied largely between the patients. The large interpatient variability in plasma pharmacokinetics after intrapleural treatment is in agreement with the findings of other studies [25]. Differences in pleural cavity volume and surface area, its physical properties (amount of tumour infiltration) and protein concentration of the effusion are factors that may partly explain this variability between the patients.

Clinical observations support the idea of mitoxantrone being a drug with favourable pleura to plasma ratio with only 1 patient displaying a leucocyte count slightly below the normal limit. This patient had previously been treated with several cytotoxic regimes and may have had a reduced bone marrow capacity. Tolerability of the drug was otherwise good with no evidence of other possible drug adverse effects.

In contrast, treatment with mepacrine chloride was associated with significant clinical morbidity. 4 of the 14 patients displayed signs of hepatotoxicity. All had fever in relation to treatment and suffered more pain with a greater need for analgesics. The therapeutic window for mepacrine is also known to be small as severe side-effects, such as convulsions, have been reported after a dose of 600 mg [26].

10 out of the 14 patients in the mepacrine group had suction treatment compared with only 1 in the mitoxantrone group. We do not believe this to be the explanation for the increased pain displayed in the mepacrine group. In contrast, most of the patients seemed to tolerate the drainage tube easily, whether suction therapy was used or not. The pain was mainly felt to be related to the reaction induced by the drug itself. The frequent use of suction therapy in the mepacrine group was instituted, mainly to secure a high response rate in that group. The procedure was also in accordance with usual practices in several centres in Scandinavia. The objective response rate to treatment, as revealed by chest radiography, was also expectedly high in the mepacrine group.

Surprisingly, the patients in the mitoxantrone group had a similarly high complete response of over 80%. There have been few published studies of mitoxantrone used locally for malignant pleural effusions. Maiche and associates have reported a response rate of 67%, similar to the effect of bleomycin in a study of these two agents in 29 patients [27]. Groth and coworkers did not find any difference between mitoxantrone and placebo (chest tube drainage alone with instillation of isotonic saline) with respect to response, response duration and survival time in a study of 103 patients [28].

The reasons for the different response rates in these studies are not clear. All the patients selected for the present study had newly diagnosed effusions, and in no patient was the effusion secondary to intrapulmonary tumour and/or atelectasis. The pleural space was generally easy to empty with re-expansion of the lung, thus preventing osmotic mechanisms from maintaining the effusion. Thus, our data in some respects emphasise the necessity of early intervention with local cytostatic treatment instead of repeated thoracocentesis.

These patients did not only report less discomfort during treatment with mitoxantrone compared to mepacrine, but also reported an improved state of general well-being at follow-up. Surprisingly, even though the chest radiography evaluation showed a similar response rate between the groups, the mitoxantrone treated group reported less dyspnoea on exertion. One should keep in mind that the initial dyspnoea score was higher in this group. However, 4 weeks after treatment, the relative differences in dyspnoea scores and the absolute scores were significantly different. The reason for these differences is not known. From the results, it may be concluded that the appearance on chest X-ray alone is not enough to predict whether or not patients will have a great relief of dyspnoea after removal of the pleural fluid. Different degrees of perfusion/ventilation mismatch in the lung parenchyma as well as differences in compliance should be taken into account. Unfortunately, we did not perform any lung function testing before or after the treatment and this should be a target for future studies. The action of the drugs are also different. While mitoxantrone has an antitumoural effect, mepacrine mainly acts by causing inflammation in the pleura. It is possible that the antitumoural effect, by limiting the local tumour burden, could improve the general well-being and as such, give a feeling of less asthenia and less dyspnoea.

In summary, we conclude that mitoxantrone is as effective as mepacrine in the treatment of malignant pleural effusion. However, mitoxantrone has the advantage of being less toxic, and more importantly, it causes less discomfort to the patient. It has a favourable pleura to plasma ratio and the risk of systemic toxicity seems to be minor. Careful patient selection is probably important in order to achieve a high response rate. Future studies are warranted in order to explore the mechanisms of action of mitoxantrone in malignant pleural effusions.


1. van de Molengraft FJ, Vooijs GP. The interval between the diagnosis of malignancy and the development of effusions, with reference to the role of cytologic diagnosis. *Acta Cytol* 1988, **32**, 183–187.
2. Gravelyn TR, Michelson MK, Gross BH, Sitrin RG. Tetracycline pleurodesis for malignant pleural effusions. A 10-year retrospective study. *Cancer* 1987, **59**, 1973–1977.
3. Sherman S, Grady KJ, Seidman JC. Clinical experience with tetracycline pleurodesis of malignant pleural effusions. *South Med J* 1987, **80**, 716–719.
4. Mejer J, Marner M, Mortensen K, Hansen HH. Mepacrine hydrochloride in the treatment of malignant pleural effusion. A controlled randomized trial. *Scand J Resp Dis* 1977, **58**, 319–323.
5. Karnofski DA, Abelmann WH, Craver LF. The use of nitrogen mustards in the palliative treatment of carcinoma: with particular reference to bronchogenic carcinoma. *Cancer* 1948, **1**, 634–642.
6. Taylor L. A catheter technique for intra-pleural administration of alkylating agents: a report of ten cases. *Am J Med Sci* 1962, **244**, 706–710.
7. Kefford RF, Woods RL, Fox RM, Tattersall MHN. Intracavitary adriamycin, nitrogen mustard and tetracycline in the control of malignant effusion. *Med J Aust* 1986, **2**, 447–448.
8. Holoye PY, Jeffries DG, Dhingra HM, *et al.* Intrapleural etoposide for malignant effusion. *Cancer Chemother Pharmacol* 1990, **26**, 147–150.
9. Luh KT, Yang PC, Kuo SH, Chang DB, Yu CJ, Lee LN. Comparison of OK-432 and mitomycin C pleurodesis for malignant pleural effusion caused by lung cancer. A randomized trial. *Cancer* 1992, **69**, 674–679.
10. Kudoh S, Takifugi N, Ryu S, *et al.* Response and pharmacokinetics of cisplatin instilled into the pleural cavity. *Gan To Kagaku Ryoho* 1985, **2**, 2161–2165.
11. Fujii M, Kiura K, Okabe K, Toki H. Intrapleural chemotherapy with cisplatin and adriamycin in lung cancer with carcinomatous pleuritis. *Gan To Kagaku Ryoho* 1986, **13**, 3203–3206.

12. Rusch VW, Figlin R, Godwin D. Intrapleural cisplatin and cytarabine in the management of malignant pleural effusions: a Lung Cancer Study Group trial. *J Clin Oncol* 1991, **9**, 313–319.
13. Moores DW. Malignant pleural effusion. *Semin Surg Oncol* 1991, **18**, 59–61.
14. Koldsland S, Svenevig JL, Lehne G, Johnson E. Chemical pleurodesis in malignant pleural effusions: a randomised prospective study of mepacrine versus bleomycin. *Thorax* 1993, **48**, 790–793.
15. Hamed H, Fentiman IS, Chaudary MA, Rubens RD. Comparison of intracavitary bleomycin and talc for control of pleural effusions secondary to carcinoma of the breast. *Br J Surg* 1989, **76**, 1265–1267.
16. Hartman DL, Gaither JM, Kesler KA, Mylet DM, Brown JW, Mathur PN. Comparison of insufflated talc under thoracoscopic guidance with standard tetracycline and bleomycin pleurodesis for control of malignant pleural effusions. *J Thorac Cardiovasc Surg* 1993, **105**, 743–747.
17. Sugitachi A, Takatsuka Y, Kido T, Miyaji N, Satoh E. Bio-adhesio-chemo (BAC) therapy for patients with malignant pleural effusion. *Am J Clin Oncol* 1989, **12**, 156–161.
18. Musch E, Loos U, Mackes KG, *et al.* Intrapleural mitoxantrone in the treatment of malignant pleural effusion. In Kreidler J, Link KH, Aigner KR, eds. *Advances in Regional Cancer Therapy. III International Conference*. Karger, Basel, 1988, 184–189.
19. Kuhn K, Purea H, Selbach J, Westerhausen M. Treatment with locally applied mitoxantrone. *Acta Med Austriaca* 1989, **16**, 87–90.
20. Larson R, Daly K, Choi K, Han D, Sinkule J. A clinical and pharmacokinetic study of mitoxantrone in acute nonlymphocytic leukemia. *J Clin Oncol* 1987, **5**, 391–397.
21. Dunne A. JANA; a new iterative polyexponential curve stripping program. *Comput Meth Programs Biomed* 1985, **20**, 269–275.
22. Gruber A, Liliemark J, Tidefelt U, *et al.* Pharmacokinetics of mitoxantrone in plasma and leukemic cells during treatment of patients with acute non-lymphocytic leukemia. *Leukemia Lymphoma* 1992, **6**, 493–496.
23. Lönnkvist PA, Bergendahl HTG, Eksborg S. Pharmacokinetics of clonidine after rectal administration in children. *Anesthesiology* 1994, **81**, 1097–1101.
24. Faulds D, Balfour JA, Chrisp P, Langtry HD. Mitoxantrone—a review of its pharmacodynamic properties, and therapeutic potential in the chemotherapy of cancer. *Drugs* 1991, **41**, 400–449.
25. Blöchel-Daum B, Eichler HG, Rainer HG, *et al.* Escalating dose regimen of intraperitoneal mitoxantrone; phase I study—clinical and pharmacokinetic evaluation. *Eur J Cancer Clin Oncol* 1988, **24**, 1133–1138.
26. Bordal KM. Convulsions following intrapleural administration of quinacrine hydrochloride. *JAMA* 1967, **201**, 173.
27. Maiche AG, Virkkunen P, Kontkanen T, Moykkynen K, Porkka K. Bleomycin and mitoxantrone in the treatment of malignant pleural effusions. A comparative study. *Am J Clin Oncol* 1993, **16**, 50–53.
28. Groth G, Gatzemeier U, Haussingen K, *et al.* Intrapleural palliative treatment of malignant pleural effusions with mitoxantrone versus placebo (pleural tube alone). *Ann Oncol* 1991, **2**, 213–215.

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