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The main purpose of our study was to develop a method having a satisfactory accuracy and precision and, at the same time, beeing sufficiently easy to be used in routine clinical work.

SUMMARY

A simple method for the dosage of glycerophospholipids in amniotic fluid is described. The method is based on liberation of glycerol from the phospholipidic molecule by means of the combined action of phospholipase C and KOH; this is followed by enzymatic determination of glycerol.

The new method is compared with phospholipid dosage by means of the traditional method using extraction and thin layer chromatography.

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Chemoprophylaxis in trophoblastic disease

by

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It is known that recurrences occur, also in the form of metastases, in about 20% of cases of hydatidiform mole ([3, 6, 11]). Nevertheless, prophylaxis by means of antiblastic chemotherapy in the pre- and post-evacuation treatment of hydatidiform mole is still controversial, both as regards its real efficacy ([19]) and as regards the advisability of administering potentially toxic agents (methotrexate, actinomycin D and others) to patients who, in the majority of cases, should run a benign post-molar course ([3, 6]). On the other hand, the view expressed by various authors ([14, 15, 16, 18]) is that chemoprophylaxis in trophoblastic disease is really effective on various technical grounds and according to incontestable clinical data, even when administered in low doses, thus avoiding all the toxicity risks of these substances. In fact, it is not necessary to make use of high (and thus toxic) doses of antiblastic agents in order to achieve effective chemoprophylaxis, but the doses

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should be in direct proportion to the quantity of trophoblastic tissue present ([15]) and to the initial titre of HCG ([8]), which is the expression of its activity.

It is also necessary to have recourse to chemoprophylaxis when faced with conditions in which there is considerable proliferation of the trophoblastic epithelium (groups IV, V and VI of Hertig & Sheldon's classification of the trophoblastic tumours, 1947).

During the course of the present investigation we took into consideration 22 cases of hidatidiform mole treated in hospital at Padua from 1965 to 1968 and from 1974 to 1975, and at Verona from 1970 to 1974, together with 479 cases described in the literature.

Our clinical experience and the data from the literature confirm, in our opinion incontrovertibly, the validity of chemoprophylaxis in trophoblastic disease, and this appears to be clear not only from the statistical significance of the differences in clinical development, and as regards the cases given chemoprophylaxis, in which the incidenze of persisting disease and the recurrence even of highly malignant illness has been markedly reduced.

Goldstein, in his clinical experience with chemoprophylaxis (1971-1974), which comprised a total of 174 cases treated, reported that he found no toxic reaction due to the antiblastic agent used (actinomycin D), and noted a significantly lower incidence of haemorrhage, sepsis and perforation in the cases treated as compared to the controls. We therefore thought it would be of interest, guided by our own clinical experience, to assess the case-histories reported in the literature, in order to obtain the best possible results.

Tables 1 and 2 show diagrammatically the results of chemoprophylaxis as they appear from the literature we consulted.

From a summary of these (Table 3) it is clear that chemoprophylaxis significantly reduces the incidence of metastatic complications, the possible error being between 5-10% ($X_2 = 3.492$) and significantly reduces the incidence of non-metastatic complications, with a probable error markedly less than 4.5‰ o ($X_2 = 32.284$).

Tab. 1. *Chemoprophylaxis in trophoblastic disease.*

Author	with chemoprophylaxis				without chemoprophylaxis			
	n. of cases	+	— with metastases	— without metastases	n. of cases	+	— with metastases	— without metastases
Koga e Maeda 1968 (1)	146	140	3	3	42	38	3	1
Goldstein 1971 (2)	73	67		6	116	93	5	18
Villegas 1973 (5)	114	106	8		53	47	6	
Goldstein 1974 (3)	100	98		2	100	84	4	12
Curry 1975 (5)	24	20	1	3	313	249	11	53
Gamerre 1975 (4)	22	20		2				
totale	479	451	12	16	624	511	29	84
%		94	2,5	3,5		81,8	4,6	13,4

(1) methotrexate: 10 mg/day orally for 7 days
(2) methorexate: 0.3 mg/kg/day i.m. for 5 days+actinomycin D –
high – 12 mg/kg/day i.v. for 5 days
low – 9 mg/kg/day i.v. for 5 days
(3) actinomycin D: 12 mg/kg/day i.v. for 5 days, within 3 days of evacuation
(4) methotrexate: 0.6 mg/kg/day by intra-arterial infusion.
(5) methotrexate

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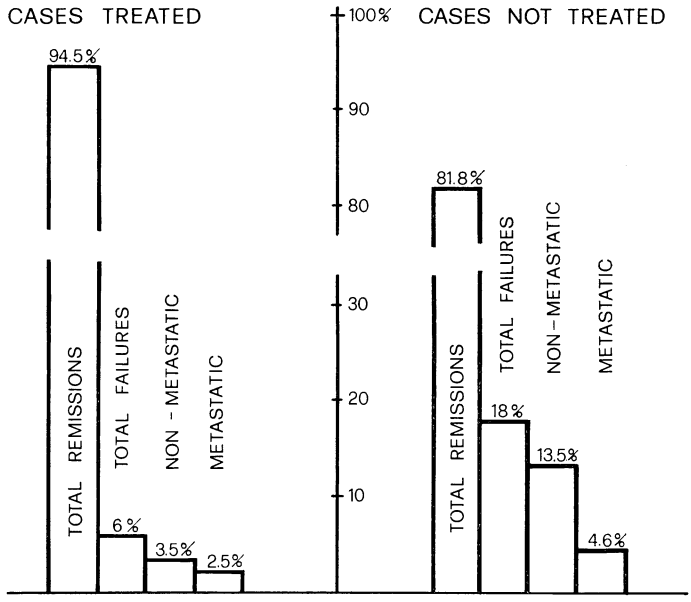
Tab. 2. *Findings in world literature on the efficacy of chemoprophylaxis in trophoblastic disease.*



Tab. 3. *Chemoprophylaxis in trophoblastic disease.*

Cases	n.	cured	not cured	
			with metastases	without
treated	479	451	12	16
not treated	624	511	29	84
statistical significance			$X^2=3,492$	$X^2=32,284$

Chemoprophylaxis significantly reduces the incidence of *metastatic complications* with a probability of error between 5-10%, and the incidence of *non-metastatic complications* with a probability of error markedly less than $0.5\,^0/_{00}$.

From an analysis of the case-histories taken into consideration, (Table 2) it seems equally evident that the drugs of choice in chemo-prophylaxis (as in the chemotherapy of malignant trophoblastic forms) are methotrexate and actinomycin D.

It is also interesting to find that the doses used by different authors are certainly less than the usual therapeutic doses, with consequent minor incidence of toxic phenomena. In assessing the results obtained with these doses, out of an aggregate (treated cases and controls) of more than a thousand hydatidiform moles, there is no difficulty in concluding, in our opinion, that there is no need to make use of high and thus toxic and dangerous doses and that therefore the chemoprophylaxis administred is absolutely harmless to the patient.

In addition the choice of drug seems to be decisive as regards the efficacy of chemophophylaxis, as was shown by the experience of Koga & Maeda (1968). These authors treated a group of patients with methotrexate and a second group

with other antiblastic agents (nitrogen mustard; thio TEPA; cyclophosphamide; mitomycin C; chromomycin H_3). The results of chemoprophylaxis conduced in this way showed that no case in the first group had metastatic sequelae, while the incidence of these in the second group (7.7%) was not dissimilar to that of the untreated cases (7.1%).

As regards the route of administration, some authors ([5]) favour regional intra-arterial infusion, and this has also been used in our department in various clinical situations, and has from time to time been employed for the treatment of resistant forms of chorionepithelioma limited to the pelvis, and for the treatment of hydatidiform moles during pregnancy, and in special conditions of risk due to other types of operation ([13]).

The massive concentration of the drug in the pelvic organs and thus directly in the trophoblastic tissue, as well as its passage into the general circulation, resulting in the development of an action in other organs and apparatus that may possibly be the site of metastases, guarantees the best results at relatively limited doses.

In our view, however, unless simultaneous arteriographic reports are indicated at the same time in some special cases, in order to assess the possible radiological malignity and pelvic spread, followed by intra-arterial pelvic infusion of methotrexate, the systemic route of administration by intravenous infusion is perfectly satisfactory in suitable cases.

Successful chemoprophylactic treatment after hydatidiform mole may further be increased simply by adequate monitoring of the general effects of the antiblastic agent: there should be a daily check on the figured elements in the blood and on the platelets; serum levels (SGOT, SGPT) should be checked; and there should be periodic radiographic controls of the thorax ([6]), with adequate follow-up procedure (Fig. 4).

Tab. 4. *Follow-up programme after hydratidiform mole.*

1. periodic clinical and radiological checks
2. oestrone-progesterone oral contraceptives for 12 months (once HCG titres negative)
3. quantitative determination of β sub-units of HCG:
(a) weekly until three consecutive normal values obtained
(b) monthly for 6 months
(c) every 2 months for 6 months

Monitoring of the urine for HCG cannot yet be taken as a certain prognostic index in cases of hydatidiform mole; it has in fact been shown ([1]) that in patient with a normal level of HCG - LH there may be several thousands of tumour cells; up to 10 I.U. of HCG may represent the production of 200,000 tumour cells for a total volume of about 0.1 cu. mm.

The problem of differentiating the quantitative analysis of HCG - LH when we have reached a normal range has however been solved recently by the possibility of determining the quantity of sub-units of HCG.

Since the chains of HCG and LH are virtually identical, analysis of the ß chains, shown to be less homologous with LH, was chosen ([2]).

By determining the ß sub-units of HCG it has thus been found possible to differentiate chorionic gonadotrophin from pituitary gonadotrophin. It is important in the follow-up to avoid administering oestrone-progesterone contracep-

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tives in order to inhibit the pituitary, in an attempt to obtain an analysis of HCG less polluted by pituitary gonadotrophin ([12]).

As has been recently demonstrated ([17]), the use of oral contraceptive before the trophoblastic tissue has completely regressed, increases the quantity of antiblastic agent required to obtain complete cure. This may also indicate that the disease is more likely to persist.

CONCLUSIONS

On the basis of the literature consulted and our own clinical experience, we draw the following conclusions:

(1) Chemoprophylaxis with methotrexate or actionomycin D in trophoblastic disease significantly reduce the incidence of metastatic and non-metastatic complications.
(2) Control of the disease should chiefly be based on the radioimmunological analysis of ß sub-units of HCG.
(3) Oestrone-progesterone oral contraceptives should be administered, if at all, only when the HCG titre is negative.

THE AUTHORS' CASES

Cases treated	22
Complete remission	21
Failure (chorionepithelioma)	1

Dosed used: Methotrexate 04mg/kg/day x 5 days.

Translated by Samil-Pabyrn foundation.

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