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INCREASED PROTEIN-BOUND IODINE IN THE SERUM FROM TOPICAL USE OF IODOCHLORO-HYDROXYQUINOLINE ("VIOFORM")

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Abstract. Nine patients were treated topically for different skin lesions with 1–3% iodochloro-hydroxyquinoline (ICHQ) ointment. Blood tests during or after treatment showed increased serum protein-bound iodine (PBI) in all cases. In 4 females, 3% ICHQ ointment was applied under polythene occlusion on 450 cm^2 of symptom-free skin for 4 days. This raised serum PBI to above normal values in all of them (mean increase: 5.6 μg per 100 ml). In 4 controls, treated likewise with 3% chloroquinaldol ointment, serum PBI remained within normal range (mean increase: 1.1 μg per 100 ml). Serum PBI in patients treated topically with ICHQ preparations is often found within a range typical for thyroid disease and may cause erroneous interpretations from PBI tests. Hence, the authors have omitted topical use of ICHQ in favour of the iodine-free hydroxyquinoline derivative chloroquinaldol (2-methyl,5-7-dichloro,-8-hydroxyquinoline).

It is well known that oral intake of iodochloro-hydroxyquinoline ("vioform") or other iodinated quinoline derivatives (commonly prescribed as intestinal antiseptics) will increase serum protein-bound iodine (PBI) values, sometimes for an unpredictable period of time (3, 4, 5, 6, 7, 12, 13). This phenomenon is particularly disturbing to endocrinologists and biochemists using PBI determinations as a method in the assessment of thyroid function.

Iodochloro-hydroxyquinoline (ICHQ) has now for many years been widely employed by dermatologists in the topical treatment of infected dermatitis, leg ulcers and some other skin disorders (8, 9, 11). In our clinic, an ointment with 3% ICHQ in a base of 10% liquid paraffin in petrolatum has been found useful for skin ulcers, erosions and infected dermatoses. When added to fluorinated corticosteroids under plastic occlusion in the treatment of psoriasis etc., it may prevent secondary infection as well as the foul smell which is otherwise caused by bacterial decomposition.

Whereas increased serum PBI from oral ICHQ has been widely reported and commented on in the literature, less attention has been given to altered thyroid function tests resulting from topical ICHQ medication. A brief mention of this was made in a foot-note to the Year Book of Dermatology 1964–65 (1), and Caravati et al. (2) have demonstrated elevated serum PBI values after ICHQ application to diseased and healthy skin.

The present study was undertaken in order to throw some further light on how likely serum PBI is to be influenced by external dermatological treatment with ICHQ.

MATERIAL AND METHODS

Blood tests for determination of serum PBI were taken from 9 patients treated with 1–3% ICHQ ointment for various dermatological conditions. The results are outlined in Case reports 1–9.

The effect on serum PBI from ICHQ applied to clinically symptom-free skin was studied in 4 female patients, with 4 other female patients serving as controls (Table I). All of them were very slightly affected by their dermatosis, and their skin was free from clinical lesions on both thighs. On the anterior aspect of these, to an area measuring 15×15 cm on each thigh (i.e. total skin area for each patient: 450 cm^2), was applied 5 ml of a 3% ICHQ ointment (2.5 ml to each side). The areas were covered with airtight polythene occlusion. The occlusive dressings were changed after 2 days, the skin cleansed with soap and water before re-application of the same amount of ointment and occluded again for further 2 days. Then the dressings were removed, the skin cleansed and left untreated.

Table I. *Age and diagnosis of patients employed in the experiments to study the effect on serum PBI from 3% ICHQ ointment applied to symptom-free skin under plastic occlusion; all were females*

Pat. no.	Age (years)	Diagnosis
ICHQ ointment		
1	16	Atopic dermatitis
2	16	Atopic dermatitis
3	33	Discoid L. E.
4	48	Psoriasis
Controls (chloroquinaldol)		
1	18	Dermatitis of hands
2	27	Eczema of unknown cause
3	20	Psoriasis
4	51	Erythema nodosum

The ICHQ ointment had the following composition:

Iodochloro-hydroxyquinoline ("vioform")	3%
Liquid paraffin	10%
Petrolatum (yellow soft paraffin)	to make 100%

The control patients were treated in exactly the same way, with the exception that their ointment did not contain ICHQ, but an iodine-free hydroxyquinoline, i.e. 3% chloroquinaldol (2-methyl,5-7-dichloro,-8-hydroxy-quinoline) in the same base.

Blood tests for determination of PBI in serum were taken on the 2nd, 4th and 6th day; i.e. the last blood test was taken 2 days after removal of the ICHQ dressings. The results are presented in Figs. 1 and 2.

PBI determinations in the serum were performed by the Department of Clinical Chemistry, Rikshospitalet. A Technicon Auto-Analyzer was used according to the method of Riley & Gochman (10). PBI values are presented as microgram per 100 ml of serum. As undiluted serum samples were analysed, PBI levels higher than 50 could not be estimated. In such cases, the laboratory answers were: >50. The normal range of serum PBI in this laboratory is 3.5–8.0.

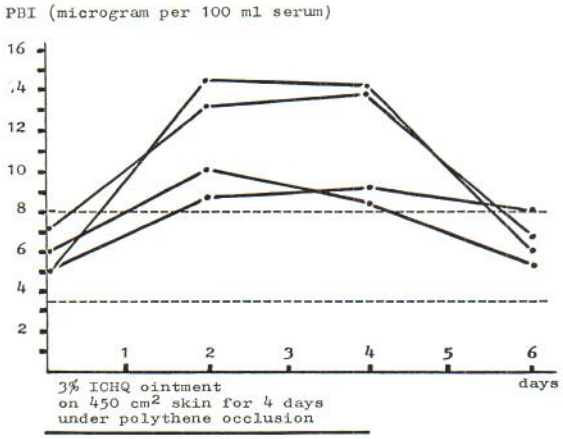

Fig. 1. Serum PBI levels in 4 females treated on symptom-free skin of both thighs with 5 ml of a 3% ICHQ ointment under plastic occlusion. The dressings were changed after 48 hours, the same amount of ointment applied for further 48 hours and then removed.

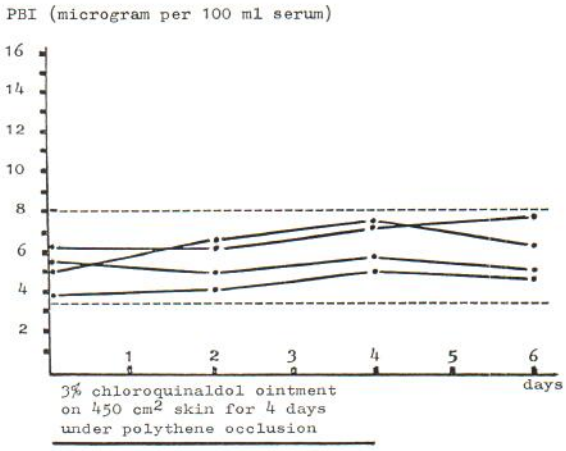

Fig. 2. Serum PBI levels in 4 females (controls) treated as the patients of Fig. 1, but with 3% chloroquinaldol ointment.

CASE REPORTS

Case 1

I. P., 59-year-old man with generalized exfoliative dermatitis (erythroderma) was admitted 1 Oct. 1968. His skin was partly eroded or ulcerated on the declive parts of the legs. He had been using 3% ICHQ ointment prior to admission. This treatment was continued until 12 Nov. and then stopped.

Serum PBI values: 7 Nov.: >50, 28 Nov.: 16.5.

Case 2

A. H., 46-year-old man with dystrophic epidermolysis bullosa causing eroded and ulcerated lesions in the axillas, gluteal and femoral regions for several years was admitted 24 Oct. 1968. He had been treated with 1–3% ICHQ ointment on and off during the last couple of years. This treatment was continued until 13 Nov. and then stopped.

Serum PBI values: 6 Nov.: *44.1*, 22 Nov.: *13.2*, 4 Dec.: *8.7*.

As from 10 Dec., daily treatment with 3% ICHQ ointment was applied to 100 cm² of eroded skin, until 26 Dec. and then stopped.

Serum PBI values: 18 Dec.: *16.8*, 27 Dec.: *19.3*, 13 Jan. 1969: *7.8*.

As from 14 Jan. to 28 Jan. 50 cm² of eroded skin was treated likewise.

Serum PBI values: 22 Jan.: *17.0*, 28 Jan.: *17.3*, 4 Feb.: *9.0*.

Case 3

I. L., 66-year-old man with generalized exfoliative dermatitis (erythroderma) of several months' duration was admitted 8 Nov. 1968. His skin displayed multiple small crusted erosions, particularly on the extremities. Topical treatment with 1% ICHQ ointment was started on 16 Nov. and stopped on 22 Nov.

Serum PBI values: 15 Nov.: *4.5,* 22 Nov.: *22.0,* 2 Dec.: *11.6.*

Case 4

S. O., 64-year-old man with psoriasis of axillas and both arms for the last year was admitted 14 Nov. 1968. Treatment of arms and legs with betamethasone-17 valerate (BMV) and 1% ICHQ in ointment was started, partly under polythene occlusion.

Serum PBI values: 15 Nov.: *5.5,* 28 Nov.: *30.*

Case 5

H. S., 18-year-old girl with dystrophic epidermolysis bullosa since infancy was admitted 19 Nov. 1968. On and off during several weeks prior to admission, she had treated eroded skin in the groins and neck area with 3% ICHQ ointment. This treatment was stopped the day she was taken into hospital.

Serum PBI values: 20 Nov.: *30.0,* 5 Dec.: *5.0.*

Case 6

M. J., 77-year-old woman with long-standing stasis dermatitis and ulcer of the left lower leg was admitted 17 Jan. 1969. The size of the ulcer was 5×6 cm. As from 18 Jan., the ulcer and surrounding skin (total area: 12×12 cm) was treated with 3% ICHQ ointment, and the dressings changed once daily.

Serum PBI values: 18 Jan.: *5.4,* 25 Jan.: *12.1.*

Case 7

K. S., 25-year-old woman with psoriasis of scalp, trunk and extremities was admitted 20 Jan. 1969. Treatment of the forearms and lower legs was started with a mixture of two parts of 0.1% BMV ointment and one part of 3% ICHQ ointment under polythene occlusion for 4 days and then stopped (treated skin area: 400 cm^2).

Serum PBI values: day 0: *5.8,* day 2: *>50,* day 4: *>50,* day 7: *13.7,* day 12: *9.0.*

Case 8

L. M. A., 41-year-old woman with long-lasting generalized psoriasis was admitted 13 Feb. 1969. Two parts of 0.1% BMV ointment was mixed with one part of 3% ICHQ ointment and applied to both hands for 48 hours under polythene occlusion. Then the dressings were removed and all further treatment with ICHQ stopped.

Serum PBI values: day 0: *5.0,* day 2: *18.9,* day 6: *6.6.*

Case 9

B. N., 50-year-old woman with lichenified stasis dermatitis and a very small ulceration on right lower leg was admitted 18 Feb. 1969. Topical treatment with 3% ICHQ ointment under polythene occlusion was applied for 4 days and then stopped.

Serum PBI values: day 0: *5.4,* day 7: *>50.*

DISCUSSION

Iodochloro-hydroxyquinoline (ICHQ) evidently interferes with the serum level of PBI, not only after oral medication, but also when incorporated into topical dermatological remedies and applied to diseased skin. The rise in serum PBI from such treatment is potentiated by erosions, ulcerations and plastic occlusion, and is accelerated by enlarging the area of skin treated.

Four days application of 3% ICHQ ointment under polythene occlusion to the lower leg in case 9 was followed by a serum PBI still above 50 μg per 100 ml 3 days after the treatment was stopped. In case 7, treatment of psoriasis on forearms and lower legs with a mixture of a steroid ointment and a 3% ICHQ ointment under polythene occlusion, caused a most striking increase of serum PBI from 5.8 to above 50 μg per 100 ml in the course of only 2 days. The treatment was stopped on the 4th day, and within the next 8 days, serum PBI dropped to 9.0.

The smaller the area of skin treated and the shorter the period of ICHQ treatment, the shorter is evidently the time required for normalization of serum PBI, which in case 8 dropped from 18.9 to 6.6 in the course of only 4 days.

When ICHQ had been given orally, Levin et al. (5) found that following discontinuation of intake, the serum PBI level required several weeks to return to the normal range. Sönksen et al. (12) found a mean serum PBI of 118 μg per 100 ml after the administration of 500 mg of ICHQ daily by mouth to 8 persons for 2 weeks, and PBI then fell slowly with a biological half-life of $2\,^1/_2$ weeks. Consequently, these authors found it advisable to allow at least 3 months to pass after oral medication with ICHQ before accepting serum PBI as a true index of thyroid function.

Judged from the present material, an allowance of 4 weeks might seem sufficient in most cases for normalization of serum PBI after discontinuation of external dermatological treatment with ICHQ preparations. However, Caravati et al. (2) suggested an allowance of 8 weeks. One of their patients had a serum PBI of 15.5 when treated topically with an ICHQ cream for 49 weeks. The PBI level was still 10.3, 5 weeks after stoppage of treatment, and after further 3 weeks, it had dropped to 5.4.

That the ICHQ molecule easily penetrates skin

which is free from pathological lesions, when covered with plastic occlusion, was clearly demonstrated by the present investigation. Three per cent ICHQ ointment under occlusion on 450 cm^2 symptom-free skin for 4 days induced a rise of serum PBI to above the normal range in all 4 subjects investigated (mean increase in PBI from day 0 to day 4: 5.6). It is noteworthy that the amount of ICHQ applied to the skin of each subject was 300 mg only, i.e. slightly more than the content of a single tablet of the strength usually designed for oral medication. Rise of PBI to above normal range did not occur in any of the 4 controls (mean increase in PBI from day 0 to day 4: 1.1) (Figs. 1 and 2).

Serum PBI values above 30–50 μg per 100 ml frequently occur after oral intake of ICHQ and cannot be due to thyroid disease. External application of dermatological medicaments containing ICHQ may easily raise serum PBI just to such values which can be found in thyroid disease, thus, leading to erroneous interpretations from PBI tests.

In consequence of these experiences, we have now omitted the topical use of ICHQ in favour of the iodine-free chloroquinaldol which has turned out to be equally useful. Chloroquinaldol is probably absorbed through the skin approximately to the same extent as ICHQ, but does not interfere with the serum PBI level as a parameter for the evaluation of thyroid function.

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