Acta Dermatovener (Stockholm) 58: 407–411, 1978

ABSORPTION OF 8-HYDROXYQUINOLINES THROUGH THE HUMAN SKIN

Torkel Fischer, Christina Fagerlund and Per Hartvig

Department of Dermatology and the Hospital Pharmacy, University Hospital, Uppsala, Sweden

Abstract. The skin absorption of clioquinol and chloroquinaldol in ointment or cream base was studied in fourteen patients with widespread dermatoses. A serum concentration in the range of 0.3–1.3 μg/ml using clioquinol and 0.05–0.1 μg/ml with chloroquinaldol was reached by the second day and persisted throughout the topical treatment. The mean serum half-life of clioquinol and of chloroquinaldol was estimated to 25 and 6 hours, respectively. Local application of zinc oxide ointment after the end of the treatment chelate-bound the skin deposits of clioquinol and lowered the serum half-life to 11 hours. The mean daily urinary excretion of the applied amount of clioquinol and chloroquinaldol was 4.5 and 6%, respectively.

Since their introduction (3), the two 8-hydroxyquinolines, clioquinol (5-chloro-7-iodo-8-quinolinol) and chloroquinaldol (5, 7-dichloro-2-methyl-8-quinolinol) have found a widespread use both as topical antimycotic and as antibacterial substances for the treatment of impetigo, dermatomycosis and infected eczema.

No studies have been made on the skin absorption of these substances. However, some absorption has been shown indirectly as a rise in serum protein-bound iodine following topical application of clioquinol (18) or as a positive urine ferri chloride test falsely indicating phenylketonuria. (14). Urinary excretion has been reported once after treatment of widespread psoriasis with clioquinol ointment (9).

The subacute myelo-opticus neuropathy (SMON) syndrome has been reported as a very severe side-effect of high doses and long-term oral administration of 8-hydroxyquinolines (17). This prompted us to study the skin absorption of these substances. A preliminary report of this study has already been published (7).

SUBJECTS AND METHODS

Patients

Fourteen patients have participated in the experiments, 11 of whom had different types of eczema and 3 had erythrodermia caused by psoriasis, pityriasis rubra pilaris, or mycosis fungoides. Before the experiments the skin was graded clinically with reference to thickness, inflammation, edema, soreness and skin area involved (Table I). Patients with less than 30% diseased skin were not included in the experiment. For 5 days the patients were treated at 8 a.m. and 4 p.m. with an adjusted amount of ointment or cream containing 8-hydroxyquinoline. Eleven patients were treated with clioquinol and 3 with chloroquinaldol. Trade names of the ointments as well as their percentage content of 8-hydroxyquinoline are given in the table. Four patients were treated with zinc oxide ointment at 8 a.m. on the sixth day of the experiment (corresponding to 120 h. from the start). The arm for blood sampling and the genital area were not treated. The amount of ointment used at each application was kept almost constant. The first 2 patients in the series (nos. 1 and 9) were treated for only 3 days and have not been completely analysed. One patient (no. 11) reacted with contact eczema to clioquinol and was excluded on the second day. Urinary analysis was not performed in this patient.

Serum and urine samples

The serum concentrations of the 8-hydroxyquinolines were determined before the first topical application, during the treatment and for 4 days after (>120 h.). Venous blood samples were drawn at 0, 1, 2, 4, 8, 24, 72, 96, 98, 100, 104, 120, 122, 124, 128, 144, 168, 182 and 206 hours. In all cases the morning blood sample was drawn immediately before the first daily application of 8-hydroxyquinoline. The serum was separated and stored at −18°C until analysed, not more than 4 days later. The poor stability of clioquinol stored at room temperature has been emphasized (8). Urine was collected in 24 hour samples, in some patients during the whole experiment in others on the fourth and fifth day. The urine samples were stored at −18°C.

Analytical procedure

The serum concentrations of clioquinol and chloroquinaldol were determined by electron capture gas chromatography after extractive methylation (8). Using serum volumes of 0.1 ml, amounts as small as 30 ng/ml of 8-hydroxyquinoline could be detected. The relative standard deviation in the determination of 250 ng/ml of clioquinol was 6.6% ($n=8$).

The urinary excretion of 8-hydroxyquinoline was measured using 0.01–0.1 ml samples. The amount excreted as

Table I. *Diagnosis and skin state of patients and topical treatment with 8-hydroxyquinoline*

Patient	Sex	Diagnosis	Skin state	Ointment	Applied amount of 8-hydroxyquinoline (g/day)	Treated body area %
1	F	Psoriasis pustulosa	Erythema, pustules, atrophy	1	0.24	80
2	M	Contact eczema	Erythema, edema, excoriations	1	0.40	40
3	F	Atopic eczema	Dry, excoriated, lichenified	1	0.20	30
4	M	Light eczema	Erythema, papules, edema	2	0.34	60
5	M	Pityriasis rubra pilaris	Erythema, papules	2	0.38	60
6	M	Atopic eczema	Erythema, slight atrophy	3	0.56	70
7	F	Mycosis fungoides	Erythema, edema, slight atrophy	3	0.24	80
8	F	Disseminated neurodermatitis	Dry, excoriated, lichenified	4	0.82	40
9	M	Atopic eczema	Dry, edematous, lichenified	4	0.72	70
10	M	Atopic eczema	Dry, excoriated, slightly lichenified	4	0.48	30
11	M	Contact eczema	Erythema, papules, vesicles	5	0.96	40
12	M	Atopic eczema	Erythema, slight atrophy	6	0.76	60
13	M	Toxicodermia (drug-induced)	Erythema, oozing, scaling	6	0.72	40
14	M	Microbial eczema	Erythema, slight atrophy	6	0.48	40

Ointments and amount of 8-hydroxyquinoline:
1. Hydrocortison-Enterokinol® ointment 1%; ACO, Solna, Sweden.
2. Celestona-Valerat Chinoform® ointment 1%; Schering Corp., Kenilworth, NJ, USA.
3. Celestona-Valerat Chinoform® cream 1%; Schering Corp., Kenilworth, NJ, USA.
4. Locacorten-Vioform® ointment 3%; Ciba-Geigy AG, Basle, Switzerland.
5. Locacorten-Vioform® cream 3%; Ciba-Geigy AG, Basle, Switzerland.
6. Sterosan-hydrocortison® ointment 3%; Ciba-Geigy, Basle, Switzerland.

conjugated metabolites was determined after hydrolysis overnight at 37° at pH=4–5 with beta-glucuronidase.

RESULTS

Serum concentrations of 8-hydroxyquinoline after topical application

Clioquinol is rapidly absorbed from human skin and a mean serum concentration of 0.3 μg/ml is found within one hour after the application. The serum concentration in 2 patients during treatment are shown in Figs. 1 and 2. The serum concentrations in each patient before the morning treatment on days 2–5 were very similar in all cases (Table II). Concentrations in the range 0.3–1.3 μg/ml were obtained despite differences in diagnosis, state of skin, type of corticosteroid present, and whether an ointment or cream was used. When applying a smaller amount of clioquinol to the skin, a tendency to lower serum values was observed. After treatment the serum concentration declined and by the fourth day only negligible clioquinol concentrations were found. A serum half-life of 19–30 hours was found. In patients treated with zinc ointment the serum half-life declined to 9–14 hours. No clioquinol was detected in serum on the third day after treatment in these patients.

Chloroquinaldol was also absorbed from the skin. The serum concentrations during treatment were in the range 0.05–0.1 μg/ml. The serum half-life was estimated to 6 hours (Table II).

Urinary excretion of 8-hydroxyquinolines

The urinary excretion of clioquinol and chloroquinaldol, respectively, was measured on the fourth day, when steady-state conditions had been established. The excretion of the 8-hydroxyquinoline plus conjugated metabolites are given in Table 2. The amounts of conjugated metabolites of clioquinol and chloroquinaldol were 95 and 97% respectively of the total urinary excretion. From the amounts recovered in urine, the minimum amounts of 8-hydroxyquinoline absorbed from the skin were calculated. The amount of clioquinol recovered was 2.2–7.5% of the applied dose, with a mean of 4.5%. The mean amount of chloroquinaldol recovered was 6.0%.

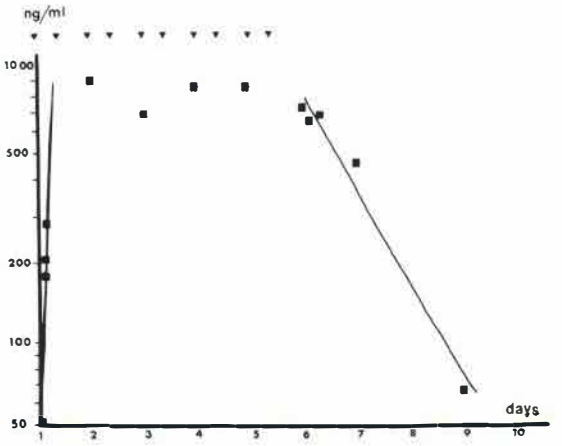

Fig. 1. Serum concentrations of clioquinol after topical application. ▼, time of application. Patient no. 8.

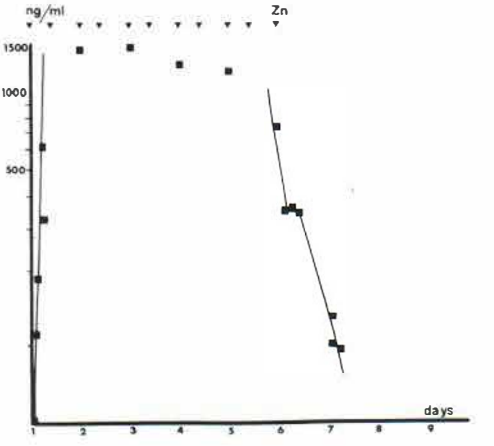

Fig. 2. Serum concentrations of clioquinol after topical application followed by zinc oxide ointment at 120 h. ▼, time of application. Patient no. 10.

DISCUSSION

Serum concentrations and elimination of 8-hydroxyquinolines

Cliquinol. After topical application, the serum concentration of clioquinol rapidly rises and continues to rise after 8 hours. From the second day and throughout treatment, the serum concentrations in all patients are maintained at a constant level, which indicates that accumulation in serum does not occur. Contrary to the findings after oral application (2), we found no conjugated clioquinol in serum after topical application.

Clioquinol absorbed from the skin passes directly into the systemic circumlation. After oral administration it first passes through the liver. Consequently a greater serum fraction of unconjugated clioquinol can be distributed to nerve tissue after skin absorption, than after absorption from the gut. Unconjugated clioquinol in serum is transferred to the nerve tissue and, owing to its lipophilic character, the concentration there may exceed that in serum (16). The lowest oral clioquinol dosage provoking a neurological symptom corresponds to a daily intake of 750 mg for 4 weeks (15). A peak serum concentration of 10 μg/ml of free clioquinol is reported after that dosage (12). The maximum serum concen-

Table II

Patient	Concentration of 8-hydroxyquinoline in serum (μg/ml). Mean of morning samples days 2–5	Serum half-life (hours)	Recovery of conjugated + unconjugated 8-hydroxyquinoline in urine (mg/day)	Absorption (%)
1	0.8	–	1[b]	–
2	0.3	18	11	2.8
3	0.4	–	9.4	4.7
4	0.5	13[a]	11	3.2
5	1.0	26	16	4.2
6	0.6	24	42	7.5
7	1.0	9[a]	14	5.8
8	0.8	30	18	2.2
9	1.3	–	–	–
10	1.2	10[a]	20	4.2
11	0.7	19	–	–
12	0.1	6	45	5.9
13	0.06	6	50	6.9
14	0.05	–	25	5.2

[a] Treatment with zinc oxide ointment at 120 h. [b] Not including metabolites.

tration reached in this study is seven times below the reported limit above which neurotoxic effects appear.

Clioquinol is stored as deposits in epidermis and is released to the systemic circulation even after the end of treatment. The range of serum half-lives of 19–30 hours is considerably longer than any previously reported (12) and indicates an uptake from skin deposits. Treatment of the skin with zinc oxide ointment inhibits the absorption of clioquinol (6). The serum concentrations of clioquinol fell rapidly and a half-life of 9–14 hours could be determined, which is in the same range as that reported after oral administration. (12) This experiment also provides evidence of a skin deposit of clioquinol after topical application.

Clioquinol is metabolized in the liver to glucuronide or sulphate metabolites (16). In man the glucuronide metabolite dominates. (10) The conjugated metabolites are excreted in the bile to the intestine, where they are hydrolysed to free clioquinol which is reabsorbed (16). Such an enterohepatic recirculation may explain the elimination curve in the patients treated with zinc ointment (Fig. 2). The main fraction of clioquinol and its conjugated metabolites are excreted in the urine (1). After oral application of clioquinol, 10–25% of the ingested amount can be recovered in the urine (1, 9, 12), and thus at least that amount is absorbed via the gut. After topical application a lower fraction or a mean of 4.5% is absorbed.

Chloroquinaldol. Although the absorption of chloroquinaldol reflected in the urinary recovery was somewhat higher than in the case of clioquinol, the serum concentrations found were considerably lower. This must be attributed to the lower serum half-life of chloroquinaldol. The serum half-life of 6 hours is in good agreement with findings after oral administration (11). Oral administration of 300 mg of chloroquinaldol resulted in a peak serum concentration of 7 μg/ml after 2 hours. A peak serum concentration appeared 2 hours after the first topical application, or much earlier than for clioquinol. Indication of an accumulation of chloroquinaldol in serum seen as an increased level during treatment could not be found.

Side effects after topical application of 8-hydroxyquinolines

Systemic absorption of topically applied 8-hydroxyquinolines has long been believed to be minimal (14, 16). The results in this study confirm that considerable amounts of 8-hydroxyquinolines are absorbed from the skin.

The most common side effect after topical application of 8-hydroxyquinolines is the contact eczema. Such an eczema may have a general flare after oral intake in a sensitized patient (4, 5). This symptom may also appear after local application, probably as a result of the absorption of the 8-hydroxyquinolines from the skin. The falsepositive protein-bound iodine test is the only documented systemic side effect from topical application of 8-hydroxyquinolines. No serious systemic side effects from local application have been reported so far.

The 8-hydroxyquinolines are effective antimycotic and antibacterial compounds when applied topically (13) and they have a given palace in the therapeutic arsenal. The absorption found in this study emphasizes that care must be taken when using the 8-hydroxyquinoline preparations for long periods and on large areas of the skin.

ACKNOWLEDGEMENT

Our thanks are due to Prof. Lennart Juhlin, Department of Dermatology and to Dr Bengt Dahlström, Department of Pharmaceutical Pharmacology, Uppsala, Sweden for valuable discussion of the manuscript.

REFERENCES

1. Berggren, L. & Hansson, O. Absorption of intestinal antiseptics derived from 8-hydroxyquinolines. Clin Pharmacol Ther *9:* 67, 1968.
2. Chen, C.-T., Kodama, H., Egashira, Y., Samejima, K., Imanari, T. & Tamura, Z. Serum levels of 5-chloro-7-iodo-8-quinolinol and its toxicity in various animals. Chem Pharm Bull, *24:* 2007, 1976.
3. David, N. A., Johnstone, H. G., Reed, A. C. & Leake, C. D. The treatment of amebiasis with iodochlorhydroxyquinoline (Vioform, N. N. R.). *100:* 1658, 1933.
4. Domar, M. & Juhlin, L. Allergic dermatitis produced by oral iodochlorhydroxyquin (Entero-Vioform®). Lancet *i:* 1165, 1967.
5. Eklund, A.-G & Möller, H. Oral provocation in eczematous contact allergy to neomycine and hydroxyquinolines. Acta Dermatovener (Stockholm) *49:* 422, 1969.
6. Fischer, T. On 8-hydroxyquinoline–zinc oxide incompatibility. Dermatologica *149:* 129, 1974.
7. Fischer, T. & Hartvig, P. Skin absorption of 8-hydroxyquinolines. Lancet *i:* 603, 1977.
8. Hartvig, P. & Fagerlund, C. Extractive alkylation of biological samples of clioquinol or chloroquinaldol and determination by electron capture gas chromatography. J Chromatogr *140:* 170, 1977.

9. Hansson, O. Acrodermatitis enteropatica. Acta Dermatovener (Stockholm) *43:* 465, 1963.
10. Haskins, W. T., Luttermoser, G. W. & Brady, F. J. The physiological disposition of diodoquin, Vioform and chinofon in the rabbit as determined with radioiodine. Am J Trop Med Hyg *30:* 599, 1950.
11. Hägermark, Ö., Wahlberg, J. E. & Germanis, M. Determination of oxyquinoline concentrations in plasma in a patient treated for acrodermatitis enteropatica—an aid in therapeutic control. Dermatologica *149:* 29, 1974.
12. Jack, D. B. & Riess, W. Pharmacokinetics of iodochlorhydroxyquin in man. J Pharm Sci *62:* 1929, 1973.
13. Konopka, E. A., Kimble, E. F., Zoganas, H. C. & Heymann, H. Antimicrobiol effectiveness of Locacorten-Vioform cream in secondary infections of common dermatoses. Dermatologica *151:* 1, 1975.
14. Neldner, K. H. The halogenated 8-hydroxyquinolines. Int J Dermatol *16:* 267, 1977.
15. Oakley, G. P. The neurotoxicity of the halogenated hydroxyquinolines JAMA *225:* 395, 1973.
16. Tamura, Z. Clinical chemistry of clioquinol. Jpn J Med Sci Biol *28*, Suppl., p. 69, 1975.
17. Toyokura, Y. & Takasu, T. Clinical features of SMON. Jpn J Med Sci Biol *28*, Suppl., p. 87, 1975.
18. Upjohn, A. C., Galbraith, H.-J. B. & Solomons, B. Raised serum protein bound iodine after topical clioquinol. Postgrad Med J *47:* 515, 1971.

Received January 23, 1978

T. Fischer, M.D.
Department of Dermatology
University Hospital
Fack
S-750 14 Uppsala
Sweden