Transient global amnesia after clioquinol
Five personal observations from outside Japan

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SUMMARY Five personal observations of an acute amnestic episode in younger individuals after intake of clioquinol are described together with three observations from the medical literature. In five of these cases the episode began after an unusually large dose, in three after a therapeutic one with a latency of about 24 hours. The clinical aspect closely resembled classical transient global amnesia but the episode after clioquinol lasted longer (24 hours to three days) and a more or less extensive retrograde amnesia persisted permanently. In one patient after three tablets of Mexase a clioquinol concentration of 12 μg/ml in plasma was found 24 hours after the specified dose, which is an unexpectedly high concentration compared to those reported as late as 24 hours after a single equal dose of Mexase or any other clioquinol-containing preparation. Another patient had a brief relapse two years after the first episode, after a single therapeutic dose of another clioquinol preparation.

Transient global amnesia, first described by Bender in 1956 and by Fisher and Adams in 1964, has received much subsequent attention and many cases have been described. We have recently analysed 70 cases, observed for up to 16 years in 63 cases (Mumenthaler et al., 1979).

In the present paper we describe five personal cases in which a transient global amnesia appeared shortly after the intake of a drug containing clioquinol. There are few reported observations of transient global amnesia after clioquinol (Kjaersgaard, 1971; Ferrier and Eadie, 1973) and experimental data concerning the effect of clioquinol in animals support our interpretation of the pathogenesis of transient global amnesia.

Case reports

Brief descriptions have already been published of case 1 (Kaeser and Wüthrich, 1970; Mumenthaler, 1970) and case 2 (Kaeser and Wüthrich, 1970). Case 4 was fully described in the general context of toxic effects of drugs by Kaeser and Scollo-Lavizzari (1970).

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CASE 1
This 24 year old college student, the daughter of a physician, had had typical migraine since her fifteenth year. She was otherwise in good health and had had no history of psychopathological episodes or drug abuse. She had made a holiday trip to Paris. On the fifth day of her visit because of diarrhoea she took Mexaform (containing clioquinol 0.2 mg per tablet) "in the prescribed dose." She has no recollection of exactly what she took but the remaining tablets found later on in the original package led to the conclusion that she took a total of six tablets. She stresses that, being a university student and a physician's daughter, she always sticks to the instructions on the packages concerning single and total doses. The next morning she was aware of some peculiar disorder of her memory. According to her companions, her behaviour seemed quite normal, perhaps somewhat more active and high spirited than usual. Feeling somewhat funny, however, she asked a companion to take her back to the hotel to get her camera. During the afternoon she took pictures and behaved normally except for some silly questions and remarks. During the next night the group made their way home to Switzerland in a bus in which she could sleep throughout
the night. Arriving home next morning, her behaviour was unremarkable and her memory was normal again. She slept, however, for the next 23 hours without interruption. While she had perfectly normal recollections from the very moment of her arrival at home there was a complete lack of memory for the whole stay in Paris—that is, for six days—and in addition there were amnestic lacunae which extended over the six preceding months. About two years later she again had diarrhoea and took two tablets of Reasec Plus (containing 0.25 mg clioquinol per tablet). Three hours later while driving her car she realised that her reactions were slowed, that she did not behave correctly in a specific traffic situation, and that she was desperately looking for her car key although she was holding it in her hand, so she went home immediately. This disturbance lasted for three hours. She never again took any drug containing clioquinol. When we saw her several years after the first episode she had normal neurological and psychiatric findings. The memory gaps for the events in Paris and the six preceding months were still present.

CASE 2

This 46 year old housewife and storekeeper had been treated two years earlier for a slight involutional depressive state. No other psychological or physical abnormalities were recorded. She made a trip to Paris with some friends. During the first six days nothing particular was observed and she behaved quite normally. On the sixth day because of diarrhoea she started taking Enterovioform (containing 0.25 mg clioquinol per tablet), a total of 18 tablets in the course of 18 hours. The next morning she was unwell and a physician was called. No precise description could be obtained about this seventh day of her visit for which the patient has a complete amnesia. She has some lacunar memory for the eighth day, although she felt that everything seemed far away, but doesn't remember anything concerning the first seven days of her stay in Paris. Seventeen days after the end of the disturbance an EEG, neurological examination and general medical examination were done, and all were normal. Three months later she still tired easily, made errors in her everyday activities, and had difficulties in remembering things. A pneumencephalogram was, therefore, done which was normal and in particular permitted exclusion of a brain atrophy. Three years later she was considered to be perfectly normal, and 15 years later she was behaving normally and had no memory problems. However, she still could not recall anything concerning the seven days of her stay in Paris. She had never taken any clioquinol-containing drug again.

CASE 3

This patient was a 34 year old housewife, a physician's wife. Her three children, sister, and mother had already taken preparations containing clioquinol. The patient herself had taken a proprietary preparation, Mexase, without any side effect. On a Friday she flew back from Israel. She remembers her arrival at the airport and being met by her husband. She was perfectly normal in her behaviour on that day and on the next two days. On the second day she had some diarrhoea and, therefore, took three tablets of Mexase in one dose (containing each 0.1 mg clioquinol and 0.01 mg phanquon). The dose is well established, and it is also certain that she did not take any other drug. In the early hours of the next morning, one day after taking the three tablets, she began to ask the same questions continuously. She was immediately put into a hospital where she continued to ask why she was in hospital, forgetting the explanations offered to her. She seemed disoriented and helpless. She could not remember details of her trip to Israel and had no recollection at all of the three days after her arrival home and before taking Mexase. Her overall behaviour, however, was coherent. Neurological and general medical findings were normal; an ECG, an EEG, and a CAT scan and spinal tap were normal. On the day of her arrival in the hospital, 24 hours after taking the three Mexase tablets, a serum sample was taken. The concentration of clioquinol on several determinations was found to be 12.05±1.14 µg/ml. We are grateful to the Department of Pharmacological Chemistry of Ciba-Geigy Laboratories, Basel, Switzerland, for these determinations, done by the method of P. H. Degen et al. (1976a, b). In the same laboratory in healthy normal individuals a serum concentration of 0.18 to 0.65 (mean value 0.38) µg/ml of clioquinol was found after the intake of the same dose of Mexase. In the same serum sample of our patient, the concentration of phanquon was also measured and this was at the level expected after the intake of three tablets of Mexase. The faculty of remembering what was said or shown to her returned on the next day in hospital and the recollections for her stay in Israel rapidly reappeared. She confirmed, however, even three months later that she still had a blank for a period of four days, not only for the day she took the tablets and the next day in hospital but also for the two days between her arrival at the airport and taking the tablets.
CASE 4
This young Australian man, a 24 year old pharmacist, had never shown mental abnormalities before. During a trip to Florence he had slight diarrhoea and, therefore, took eight tablets of Enterovioform (containing 0.25 mg clioquinol in a tablet) as a single dose. In the next 24 hours he swallowed 30 more tablets. On the next day he drove his car about 400 miles to Switzerland. In the evening he was very thirsty and was said to have drunk three litres of soda water. The next morning an acute state of disorientation began. He was alternately apathetic and excited, did not recognise his surroundings or his companions, and always asked the same questions. The acute disturbance only disappeared on the third day but a retrograde amnesia persisted which covered the whole preceding week and which diminished only partially in the subsequent weeks. Neurological examinations after four and 20 days were normal. An EEG on the first day after the beginning of the acute episode showed intermittent theta and delta waves with some sharp features bilaterally in the frontotemporal regions. These changes were still present after 20 days (for details see Kaeser and Scollo-Lavizzari, 1970).

CASE 5
This 31 year old housewife, a physician's sister-in-law, had always been in good health and had never taken clioquinol before. At the beginning of the third week of a trip to Russia she had diarrhoea which was treated with Eucarbon. On the flight back home she took two tablets of dramamine. During the first week back home in Switzerland she took no drug at all but still had diarrhoea. On the seventh day after her arrival in Switzerland a pharmacist recommended her to take three tablets of Mexaform thrice daily. The patient, whose weight was 55 kg, and her husband (85 kg) both took during the day nine tablets of Mexaform each in three doses, beginning late in the morning. The next morning she woke up with an unpleasant feeling which she could not describe exactly and she felt apathetic. At lunch she started crying and took two more tablets of Mexaform. One hour later she started to show real disturbances of behaviour, being disoriented in time, asking the same questions again and again, for example why her husband was wearing his Sunday suit. She immediately forgot what was explained to her so that her husband finally changed his dress. She had no memory of the previous four weeks and completely denied having even been in Russia. She was admitted to hospital the same afternoon where her behaviour was described as stuporous. General medical and neurological findings were normal. Her behaviour became more and more normal during the next two days and was again unremarkable when she left hospital on the fifth day. At that time, however, she still had a complete amnesia for the preceding five weeks at least, including the trip to Russia. During the next two weeks she began to remember more and more of her trip to Russia but there persisted a permanent blank in her memory for the three days before taking the first Mexaform tablet and for the two days after this. Re-examination three and a half years later confirmed the persistence of this memory gap. The psychopathological and neurological findings were normal. The husband who had also taken nine tablets in one day did not show any disturbance.

Discussion
The clinical features of transient global amnesia, as we could confirm from 70 personally observed cases (Mumenthaler et al., 1979), are quite characteristic. The patients are in general elderly and in previous good health. The disturbance starts acutely. The patients are unable to retain whatever is said or shown to them and they repeatedly ask the same questions about the time, the date, and the reason for their being in a place. They cannot keep the answers in mind and repeat the same question a few minutes later. They, therefore, seem restless and preoccupied, and sometimes also seem disoriented in time. They are, however, quite able to act apparently normally and even to execute complex activities such as cooking, driving a car, or doing professional activities. During the acute amnestic episode there is also a retrograde amnesia which can extend over the months or even years so that patients, for example, do not remember a recent trip or the birth of a grandchild. Classical transient global amnesia lasts only a couple of hours and then the faculty to retain impressions returns. In the meantime, in the course of a couple of hours, the retrograde amnestic gap is filled again. The only period which later remains “blank” is that of the acute episode itself, of several hours duration.

In the large number of papers from Japan concerning the possible side effects of clioquinol, the main attention was paid to the subacute myelo-optic neuropathy (SMON) (Sobue et al., 1971). There is, however, one article in Japanese (Ogawa et al., 1975), the only one we are aware of, dealing with acute symptoms after ingestion of clioquinol which are comparable to the ones observed by us.
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During a flood catastrophe in 1969, the district authorities distributed clioquinol tablets free of charge to the population in order to avoid dysentery. The instructions given were erroneous and people took doses which were up to five times the normal. Out of the 147 people who took the clioquinol, 33 developed "acute poisoning symptoms." The average amount of clioquinol taken by those who developed symptoms was 2.0 g while those without symptoms took 1.2 g. In 19 cases out of 33 with acute symptoms, "mental and nervous symptoms" were seen in four males and in eight females. These symptoms are only described very approximately as "serious symptoms such as convulsions, loss of consciousness, loss of orientation, and retrograde amnesia."

Outside Japan, in our own country for example, the cases in which a relationship between central nervous system symptoms and clioquinol intake has to be discussed, are extremely rare (Kaeser and Mumenthaler, 1976; Kaeser and Wüthrich, 1970). It, therefore, seemed worthwhile to describe these personal observations, which all presented outside Japan. The main characteristics of our

Table Summary of characteristics of eight patients showing a relationship between CNS symptoms and intake of clioquinol

<table>
<thead>
<tr>
<th>Case</th>
<th>Source of information</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Profession</th>
<th>Preparation and dosage</th>
<th>Latency (hr)</th>
<th>Duration of acute episode</th>
<th>Observations during acute episode</th>
<th>Signs</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kjaersgaard (1971)</td>
<td>21</td>
<td>F</td>
<td>Probationer</td>
<td>Enterovioform 16 x 0.25 mg clioquinol</td>
<td>12+night rest</td>
<td>? 3 days</td>
<td>Disoriented, confused, repeated same questions. Doesn't remember her marriage 3 months before</td>
<td>Normal neurological findings and EEG</td>
<td>Retrograde amnesia of 3 months, slowly shrinking to 1 week</td>
</tr>
<tr>
<td>2</td>
<td>Ferrier and Eadie (1973)</td>
<td>43</td>
<td>F</td>
<td>Physician's wife</td>
<td>Clioquinol 6 x 0.25 mg</td>
<td>12+night rest</td>
<td>3 days</td>
<td>Confused, restless, headache, vomiting. Always same questions</td>
<td>Normal neurological findings, spinal tap and EEG</td>
<td>Amnesia questionably only for the acute episode</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>32</td>
<td>M</td>
<td>Airline pilot</td>
<td>Clioquinol 16 x 0.25 mg</td>
<td>12+night rest</td>
<td>3 days</td>
<td>Disoriented, sleepy. Retrograde amnesia of 1 year's duration</td>
<td>Normal neurological findings, spinal tap and EEG</td>
<td>2 weeks later still partial retrograde amnesia</td>
</tr>
<tr>
<td>4</td>
<td>Our case 1</td>
<td>24</td>
<td>F</td>
<td>University student, physician's daughter</td>
<td>Mexaform 6 x 0.2 mg clioquinol</td>
<td>12+night rest</td>
<td>24 hours</td>
<td>Somewhat peculiar, essentially normal behaviour</td>
<td>Normal neurological findings, several years later</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Our case 2</td>
<td>46</td>
<td>F</td>
<td>Housewife and store-keeper</td>
<td>Enterovioform 18 x 0.25 mg clioquinol</td>
<td>12+night rest</td>
<td>24 hours</td>
<td>Altered behaviour</td>
<td>Normal neurological findings and EEG</td>
<td>Persistent retrograde amnesia for 6 months</td>
</tr>
<tr>
<td>6</td>
<td>Our case 3</td>
<td>34</td>
<td>F</td>
<td>Physician's wife</td>
<td>Mesase 3 x 0.1 mg clioquinol + 0.01 mg phanquon</td>
<td>12+night rest</td>
<td>24 hours</td>
<td>Disoriented in time</td>
<td>Normal neurological findings, spinal tap, EEG and CAT scan</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Our case 4</td>
<td>24</td>
<td>M</td>
<td>Pharmacist</td>
<td>Enterovioform 30 x 0.25 mg clioquinol</td>
<td>48+night rest</td>
<td>48 hours</td>
<td>Confused, apathetic, and excited</td>
<td>Normal neurological findings, EEG with bilateral slow waves</td>
<td>Persistent partial retrograde amnesia of 1 week duration</td>
</tr>
<tr>
<td>8</td>
<td>Our case 5</td>
<td>31</td>
<td>F</td>
<td>Housewife, doctors in family</td>
<td>Mexaform 9 x 0.2 mg clioquinol</td>
<td>26+night rest</td>
<td>48 hours</td>
<td>Disoriented in time, repeats same questions, retrograde amnesia for at least 4 weeks</td>
<td>Normal general and neurological findings</td>
<td>Persistent retrograde amnesia of 3 days persists</td>
</tr>
</tbody>
</table>

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five personal cases, and of three further cases from the medical literature outside Japan (Kjaersgaard, 1971; Ferrier and Eadie, 1973) are shown in the Table. A computer-assisted search of the medical literature for cases reported since 1975 did not disclose any further papers.

There seem to be some differences between the acute amnestic episode after clioquinol and the classical type due to transient ischaemic attack described above. Six of the eight cases after clioquinol also showed some disorientation, excitement, incoherence, and apathetic phases. Also, the duration of the episodes which were between 24 hours and three days was considerably longer than we observed in our 70 cases of classical transient global amnesia: 46 of 49 cases in which the duration could be properly defined did not last longer than 12 hours, and not one exceeded 24 hours (Mumenthaler et al., 1979). The one characteristic, however, which is different quite often in the clioquinol cases is the permanent more or less extensive retrograde amnesia which persists even many years after the acute episode. There remained a memory blank for at least a couple of days before the beginning of the episodes (and the intake of the drug). In our own first case there were also islands of amnesia distributed over several months before the acute episode. General medical and neurological examinations were always normal, even in the acute phase. This was also the case with EEG with the exception of case 4. The fact that in seven of the eight cases in the Table (in case 1 this aspect is not mentioned) the episode appeared immediately after a trip abroad has, of course, no pathogenetic importance: it is on these occasions that diarrhoea in general appears which was the reason for taking the drug. Probably it is also just by chance that five of the eight patients were either active in a paramedical profession or were living in a physician’s household and one further patient was the sister-in-law of a physician. However, this circumstance may have increased the chances of the cases being brought to the attention of specialists who tried to look more deeply into the problem. The doses taken were too high in five of the eight cases, and exceedingly high in case 4 where a tenfold daily dose was taken. The doses were, however, regular therapeutic ones in three of the eight cases. In case 6 of the Table the same drug had been taken before without any side effect. Only one patient (our first case) had taken a second preparation containing the same clioquinol two years after the first episode. This produced, with a latency of three hours, a short period of slight psychical disturbances which were appreciated by the patient.

There are several arguments in favour of a real pathogenic effect of clioquinol in the cases presented. One is the constancy of the latency between taking the drug and the beginning of the disturbance, as well as the uniformity of the clinical phenomena and of the regularly persisting memory gap of several days preceding the episode. A further argument is the incomplete and involuntary repetition in our first case after a second intake of clioquinol. Also the fact that in our case 3 a very high serum concentration of clioquinol accompanied the acute clinical phase indicates a causative relationship.

In several papers cerebral symptoms in dogs were described after the intake of Enterovioform and other clioquinol-containing drugs (Fischer, 1964; Hangartner, 1965; Schantz, 1965; Müller, 1967; Schaumburg et al., 1978). The doses were those recommended for humans which, however, represent in the generally small breeds of animals a relatively high dose to weight ratio. After an interval of at least five hours, frequently, however, after 24-48 hours, there was generally first an episode of restlessness and then repeated epileptic fits. Surviving dogs showed retrograde amnestic gaps: they failed to recognise their usual surroundings. These observations prompted a warning by the manufacturers and abandonment of the drug for veterinarian purposes. These side effects, however, were not limited to dogs: similar observations were described in cats which licked Vioform powder from the skin (Hangartner, 1965) or in experiments in monkeys (Richter, 1949; Schmidt and Schmidt, 1951), rats and mice (Roesch et al., 1965; Püschner and Fankhauser, 1969). At necropsy, selective changes were observed in the hippocampus and nucleus amygdalae (Püschner and Fankhauser, 1969).

These pathological findings as well as the clinical aspect of the veterinary observations are a strong argument for a genuine pathogenetic role of clioquinol in the appearance of the acute amnestic episodes in humans. The hippocampus and the corpora mamillaria play an important role in short-term memory. Bilateral disturbances of these structures do not disturb the ultra-short memory, but lead to the impossibility of storing new impressions for a longer time period. The same structures also play an important role for recalling stored data. We have discussed these aspects in detail in an earlier paper (Mumenthaler and von Roll, 1969). One could, therefore, easily conceive that a drug which is known to produce
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memory defects, and the general toxicity of which may be associated in animals with anatomical changes in the hippocampus, could induce acute disturbances of the short-term memory and amnesia in humans.

The question still remains as to why a drug which is taken so frequently does not produce such disturbances of memory much more frequently. This unsolved question has to be aligned with the other problem which is also poorly understood—that is why SMON, which has some relationship with clioquinol-intake, and which is so frequently observed in Japan (Sobue et al., 1971) is so rare in other countries (Selby, 1972; Wadia, 1977) including Switzerland (Kaeser and Mumenthaler, 1976). The thorough histo-pathological analysis of brains of animals experimentally intoxicated with clioquinol (Pischner and Fankhauser, 1969; Lannek and Jönsson, 1974; Krinke et al., 1978) revealed anatomical changes of ischaemic type in some of the treated animals. As a rule, the occurrence of ischaemic encephalopathy was preceded by signs of severe general intoxication, including cardiovascular and respiratory symptoms or even seizures. The mechanism by which an acute overdose of clioquinol brings about ischaemic lesions in animals is not known and, for ethical reasons, it is not possible to carry out systematic clinical trials in human beings.

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