PAPERS AND SHORT REPORTS

Amodiaquine induced agranulocytosis and liver damage

KLAUS A NEFTEL, WERNER WOODTLY, MARTIN SCHMID, PAUL G FRICK, JÖRG FEHR

Abstract

Seven cases of agranulocytosis and two of liver damage that were probably due to amodiaquine treatment were studied. In five cases agranulocytosis was combined with liver damage, and in one case of primary liver damage moderate neutropenia was present. Three patients died. High total doses or prolonged duration of treatment, or both, appear to favour the occurrence of these reactions.

The clustering of five of the seven cases of agranulocytosis within six months in one medical centre indicates that the risk to benefit ratio of amodiaquine for malaria prophylaxis should be re-evaluated.

Introduction

Amodiaquine (Camoquin, Parke-Davis) is a 4-aminoquinoline derivative used in the prophylaxis and treatment of malaria, and also for the treatment of rheumatoid diseases. Agranulocytosis[1-10] and liver damage[11 12] have repeatedly been reported as adverse reactions to amodiaquine. For reasons unknown both reactions seem to occur together more often than expected by chance.

In 1982 and 1983 we observed two patients with amodiaquine induced agranulocytosis and detected a drug dependent granulocytotoxic antibody in the serum of one of these patients.[13] Between February and July 1985 five further patients with suspected amodiaquine induced agranulocytosis were transferred to our hospital. Five out of these seven patients also had liver damage, an observation that led us to the retrospective discovery (in 1981 and 1983) of two additional patients with primary liver damage after receiving amodiaquine prophylaxis. One of these patients had moderate concomitant neutropenia, the other died of liver dystrophy after taking excessive doses of amodiaquine for five weeks after conventional malaria prophylaxis with this drug for three months. These alarming observations, made at a time of an increasing market for amodiaquine, deserve broader attention.

Case reports

Table I gives clinical data on seven patients with agranulocytosis. The lowest peripheral neutrophil counts in three patients (cases 2, 4, and 7) were 8×10^6/l, 72×10^6/l, and 73×10^6/l, respectively. Neutrophils were not detected in the remaining patients. In four patients myelopoiesis in the bone marrow aspirate was absent. In two patients only isolated myeloblasts were found, and in another, in whom bone marrow aspiration was performed 11 days after the last amodiaquine dose, myelopoiesis increased quantitatively and was present up to the myelocyte stage. Erythropoiesis was slightly megaloblastic in one patient, exhibited karyorrhexis in another, and was normal in the remainder. Megakaryopoiesis increased quantitatively in five patients and was normal in two.

TABLE I—*Clinical data on seven patients with amodiaquine induced agranulocytosis*

Case No	Sex and age (years)	Amodiaquine: Total dose (g)	Amodiaquine: Duration of treatment (days)	No of Fansidar tablets*	Time to onset of first symptom (days)	Duration of neutropenia ($<0{\cdot}5\times10^9$/l) (days)
1	M 76	3·6	49	9	49	10
2	M 71	3·2	49	8	42	10
3	F 52	3·2	49	16	51	24
4	F 64	4·0	62	10	69	45
5	F 63	3·6	49		57	11
6	F 17	6·0	63		48	33
7	M 39	1·8	34		38	8

* One tablet sulfadoxine 500 mg, pyrimethamine 25 mg.

Complications seen were those expected in cases of severe agranulocytosis, including septicaemia (in cases 1, 2, 3, and 6), single or multiple

Medical Clinic, University Hospital, 8091 Zurich, Switzerland
KLAUS A NEFTEL, MD, lecturer in internal medicine
PAUL G FRICK, MD, professor of medicine
JÖRG FEHR, MD, lecturer in haematology

Neumünster Spital, Zurich, Switzerland
WERNER WOODTLY, MD, professor of medicine

City Hospital, Waid, Zurich, Switzerland
MARTIN SCHMID, MD, professor of medicine

Correspondence and requests for reprints to: Dr Neftel.

abscesses (cases 1, 3, 5, and 6), orbital infection (case 1), and gangrene of a toe and necrotic angina (case 6). Two patients died from pseudomonas septicaemia (cases 1 and 2) and another had pulmonary embolism while agranulocytotic (case 5); this patient died from recurrent embolism three weeks after the recovery of the peripheral neutrophil count. Five patients presented with concomitant icterus or signs of liver damage, or both (table II).

Necropsy in one patient (case 2) showed a slightly enlarged, smooth liver. Postmortem needle puncture taken shortly after death showed a mild predominantly centrilobular cholestasis with noticeable imbibition of liver cells and adjacent Kupffer cells by brownish bile pigment droplets. Scanty and slender bile thrombi within minimally dilated canaliculi were difficult to detect. In some areas moderate sinusoidal dilatation was seen. Besides a mild zonal predominantly perivenular steatosis liver cells were normal. Clusters of liver cells containing fat droplets of varying size arranged around sclerotic central veins may represent pre-existing alcoholic damage rather than a recent toxic lesion. Portal tracts showed moderate mononuclear infiltration intermingled by few neutrophilic granulocytes. A conspicuous lesion was seen in the interlobular bile ducts and ductules. The epithelium was swollen with light, vacuolated, and sometimes foamy cytoplasm (fig 1).

One patient (case 4) drank a moderate amount of alcohol. The other patients had no known risk factors for liver damage or history of pre-existing liver disease.

A retrospective chart survey detected two additional patients (case 8, seen in 1981, and case 9, 1983), who presented with isolated hepatotoxicity after taking amodiaquine (table III). The patient in case 8 was first seen 12 days after taking the last amodiaquine dose. At this time his peripheral neutrophil count was $0{\cdot}49\times10^9$/l but increased to $3{\cdot}06\times10^9$/l within 48 hours. These findings suggest recovery from agranulocytosis. The patient in case 9 developed scleral icterus after taking 400 mg amodiaquine weekly for three months as malaria prophylaxis. To treat suspected malaria she took a single dose of 1200 mg amodiaquine followed by three doses of 200 mg amodiaquine each week for five more weeks. During this time icterus increased progressively. She was transferred to our hospital with initial hepatic failure and died 17 days later.

At necropsy submassive liver necrosis was found (fig 2). The distance between the central vein and portal tract had shortened. Most of the cells were no longer visible, and shadows of resting parenchyma were confined exclusively to periportal areas. Although this patient had a disproportionately high serum bilirubin concentration, liver tissue showed only moderate and even mild cholestatic features. Few bile lakes were seen in the shadows of parenchyma. Clusters of macrophages contained bile pigment, and dense bile was seen within the lumina of the bile ducts and ductules. Proliferated bile ducts and ductules were embedded in a loose portal infiltrate consisting of neutrophilic and sometimes eosinophilic granulocytes and clusters of mononuclear cells.

Four patients (cases 1, 2, 3, and 4) had taken Fansidar (sulfadoxine 500 mg and pyrimethamine 25 mg in each tablet) simultaneously with amodiaquine, as shown in table I. One of these patients (case 3) had received two intramuscular injections of a combination of phenylbutazone, carbamoylphenoxyacetic acid, dexamethasone, and lignocaine 15 and 13 days before onset of the first symptom. Five patients (cases 1, 4, 7, 8, and 9) had previously received malaria prophylaxis, including various 4-aminoquinolines, but one patient only had previously received amodiaquine. With the exception of headache and nausea the patients had experienced no side effects during previous prophylaxis.

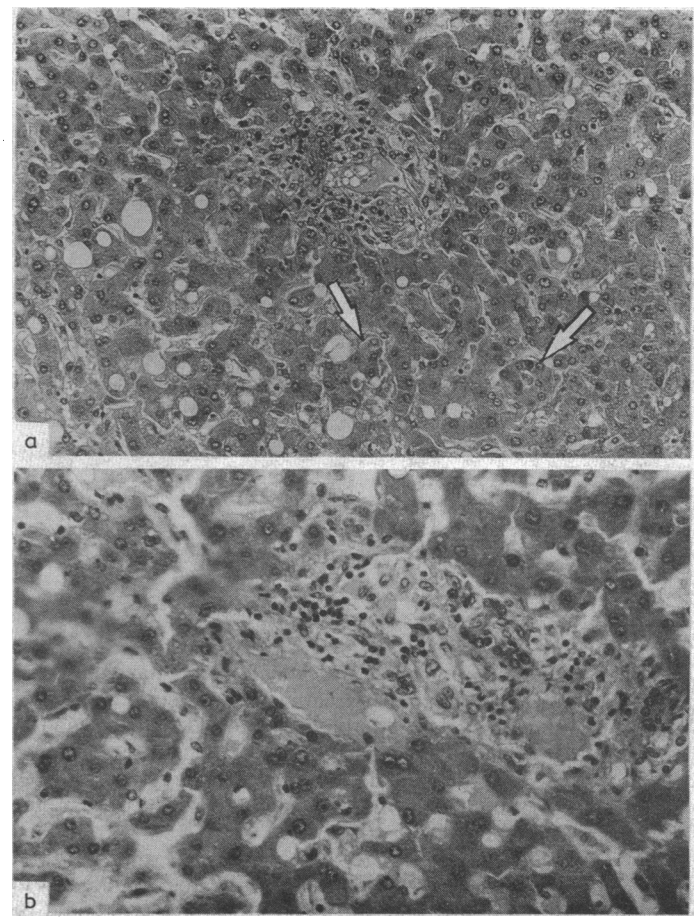

FIG 1—Postmortem specimen from patient in case 2. (*a*) Small portal tract with scanty mononuclear infiltration and small bile ducts showing swollen, light epithelium. A few bile plugs are surrounded by pseudoacinar arranged liver cell rosettes (arrows). (*b*) Portal tract with conspicuous bile duct alteration. (Haematoxylin and eosin.)

TABLE II—*Serum liver enzyme activities and bilirubin concentration in five patients with liver damage and agranulocytosis*

Case No	Alanine aminotransferase (60 U/l)*	Aspartate aminotransferase (60 U/l)*	Alkaline phosphatase (115 U/l)*	γ-Glutamyl-transferase (50 U/l)*	Bilirubin (22 μmol/l)*	Normalisation (days)
2	Normal	Normal	Normal	Not done	91	Died
3	Normal	Normal	165	226	37	5
4	Normal	Normal	480	310	Normal	18
5	Normal	Normal	458	344	110	21
7	950	1690	212	Not done	214	28

* Upper normal limit.
Conversion: SI to traditional units—Bilirubin: 1 μmol/l≈0·06 mg/100 ml.

TABLE III—*Clinical data on two patients with hepatotoxicity after amodiaquine treatment*

Case No	Sex and age (years)	Amodiaquine: Total dose (g)	Amodiaquine: Duration of treatment (days)	Alanine aminotransferase (60 U/l)*	Aspartate aminotransferase (60 U/l)*	Alkaline phosphatase (115 U/l)*	γ-Glutamyl-transferase (50 U/l)*	Bilirubin (22 μmol/l)*
8	M 55	2·2	42	142	Normal	126	69	49
9	F 36	9·4	120	651	726	166	Not done	830

* Upper normal limit.
Conversion: SI to traditional units—Bilirubin: 1 μmol/l≈0·06 mg/100 ml.

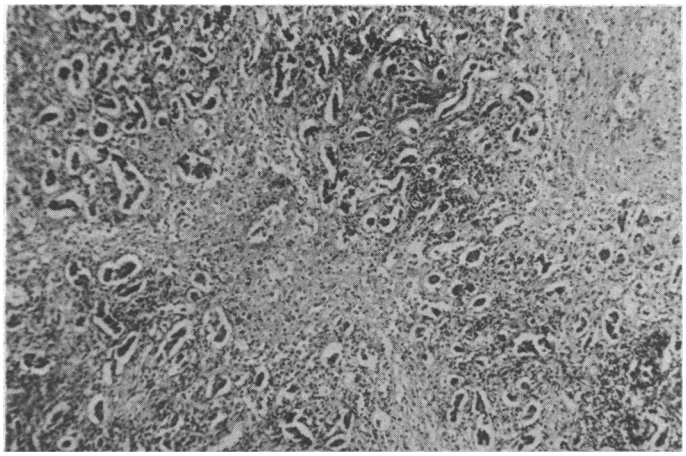

FIG 2—Postmortem specimen from patient in case 9 showing massive liver necrosis and noticeable bile duct proliferation. (Haematoxylin and eosin.)

Discussion

Since 1953, 15 cases of amodiaquine induced agranulocytosis have been reported.[1-10] Their clinical and laboratory presentation of all reported cases match perfectly with our seven cases, the most prominent features being the dose or time dependent occurrence of agranulocytosis, or both, and the concomitant liver damage. Of the patients in the earlier reported cases, only five developed agranulocytosis as a result of malaria prophylaxis regimens and the first symptoms were not seen until the sixth week of treatment. The remaining patients received much higher doses for treatment of malaria or rheumatoid diseases. Hence the total amodiaquine dose, which always exceeded 1·5 g in adults, might be more important than the duration of treatment, which varied between six days and more than three months. This observation favours a toxic rather than immune mediated mechanism. 4-Aminoquinolines accumulate noticeably in both leucocytes and liver tissue[14] and, moreover, inhibit protein synthesis in cultured mammalian cells.[15] Such phenomena could explain selective bone marrow and liver toxicity. Thus the amodiaquine dependent granulocytotoxic antibody that we found in the serum of one patient (case 6) might be an unrelated concomitant of amodiaquine treatment.[13]

With no reliable in vitro test available the cause and effect relation remains unknown. The uniform clinical presentation and course of agranulocytosis, however, suggest amodiaquine to be the common denominator.

The local clustering of five cases of amodiaquine induced agranulocytosis within six months raises questions about the incidence and epidemiology of this drug reaction. If we assume that our medical centre has a maximum referral area with one million inhabitants about 30 000-35 000 of these subjects are expected to require malaria prophylaxis during a period of six months (Swiss Federal Office of Statistics). In Switzerland the number of prescriptions for amodiaquine for this purpose has increased about threefold within the past five years (written communication by the manufacturer) and make up about 15% of the antimalarial market (R Steffen, University of Zurich, personal communication). Hence the five cases seen in 1985 might indicate a higher incidence of amodiaquine induced agranulocytosis than previously expected and probably reflect the increased use of this drug in Switzerland.

Agranulocytosis has been described as a consequence of treatment with various 4-aminoquinolines other than amodiaquine.[16] Although in Switzerland some of these compounds have been used more often than amodiaquine, no such reactions have been registered by the Swiss Drug Monitoring Centre.

Amodiaquine induced liver damage, though mentioned repeatedly in published reports, remains poorly explained.[11 12] Pomeroy *et al* published a report of a patient with "suggestion of pre-existing liver disease" who died in hepatic coma after treatment with amodiaquine 200 mg daily for 16 weeks.[12] In our patients an association of amodiaquine induced agranulocytosis with liver damage was evident. Clinical and laboratory findings were predominantly characterised by cholestatic jaundice without pruritus. Compared with the mild cholestatic variables serum bilirubin concentration was disproportionately high in several cases. Noticeable bile duct alteration was noted in one patient (case 2), but unfortunately no liver biopsy examination could be performed. Liver tissue taken after death confirmed the clinically expected moderate cholestatic features in both cases 2 and 9. These mild to moderate cholestatic lesions resemble the morphological findings in cases of benign postoperative jaundice,[17] called bilirubinostatic icterus by some authors.[18]

The choice of an optimal malaria prophylaxis remains a concern for the large population travelling to regions where the disease is endemic. In the face of increasing numbers of prescriptions for amodiaquine the question arises whether the risk to benefit ratio ascribed to this drug remains acceptable.

A study by Hatton *et al* published in February described another seven cases of amodiaquine induced agranulocytosis.[19] This report has prompted the manufacturer (Parke-Davis) to write to doctors and pharmacists in the United Kingdom and to revise the data sheet for Camoquin. The manufacturer is also seeking to change Camoquin to a prescription only medicine.

The data sheet changes are as follows: (1) The prophylactic use of amodiaquine as a first line agent has been restricted to chloroquine resistant areas. (2) In all but one of the cases reported amodiaquine had been used in combination with proguanil. The warning about agranulocytosis now reads: "Agranulocytosis has occurred in association with the use of amodiaquine in malaria prophylaxis. Although agranulocytosis has been reported following the sole use of amodiaquine, most cases have occurred when other anti-malarials have been taken concurrently. Therefore, the prescribing physician should assess the advantages and disadvantages of amodiaquine in malaria prophylaxis but if the decision is made to so prescribe the drug, concomitant use with other anti-malarials should be avoided and regular laboratory investigations should be performed to assure that blood values and liver function tests remain within normal limits." (3) The recommended dosage has been reduced to 400 mg a week for adults and 7 mg/kg a week for children (15 years and younger) when used for malaria prophylaxis.

In its bulletin of 12 December 1985 the Swiss Federal Office of Public Health informed practitioners about the present matter. Since observing the above cases, four further cases of agranulocytosis and two of hepatitis probably due to amodiaquine have been communicated to the office. These cases matched the clinical features of the cases presented here.

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