Amodiaquine induced agranulocytosis and liver damage

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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. Agranulocytosis1-8 and liver damage9-12 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 granulocytopoietic 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 x 10⁹/l, 72 x 10⁹/l, and 73 x 10⁹/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 karyorhexis in another, and was normal in the remainder. Megakaryopoiesis increased quantitatively in five patients and was normal in two.

Complications seen were those expected in cases of severe agranulocytosis, including septicemia (in cases 1, 2, 3, and 6), single or multiple
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
agranulocytic (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 centrolobular 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 perivascular 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 hepatocytotoxicity 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 0·49 x 10³/µl but increased to 3·06 x 10³/µl 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 perportal 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 lumen 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,
carbamoylphenoxycetic acid, dexamethasone, and linogocaine 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-amino-
quinolines, 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. (Haemato-
oxycin and eosin.)](http://www.bmj.com)  

| TABLE II—Serum liver enzyme activities and bilirubin concentration in five patients with liver damage and agranulocytosis |
|---|---|---|---|---|
| Case No | Alanine aminotransferase (U/l)* | Aspartate aminotransferase (U/l)* | Alkaline phosphatase (115 U/l)* | γ-Glutamyltransferase (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 |
| 6 | 590 | 212 | Not done | 214 | 28 |

* Upper normal limit.

Conversion: 51 to traditional units—Bilirubin: 1 µmol/l=0·06 mg/100 ml.

| TABLE III—Clinical data on two patients with hepatocytotoxicity after amodiaquine treatment |
|---|---|---|---|---|
| Case No | Sex and age (years) | Amodiaquine | Total dose (g) | Duration of treatment (days) | Alanine aminotransferase (U/l)* | Aspartate aminotransferase (U/l)* | Alkaline phosphatase (115 U/l)* | γ-Glutamyltransferase (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: 51 to traditional units—Bilirubin: 1 µmol/l=0·06 mg/100 ml.
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,¹⁰ called bilirubinostatic icterus by some authors.¹⁰

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.¹⁶ 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 diagnosis of agranulocytosis is made on the basis of blood count below 1-0 x 10⁶/l neutrophils, although persistent agranulocytosis also occurs with amodiaquine at therapeutic levels. The drug is indicated for chemoprophylaxis and not for the treatment of malaria. The use of amodiaquine has increased about 4-fold in the last 5 years and it is also being used in a number of endemic areas as an alternative to chloroquine in areas where chloroquine-resistant Plasmodium falciparum is present. The use of amodiaquine has also increased the number of patients with agranulocytosis.

In the UK the number of reports of agranulocytosis associated with amodiaquine has increased from 2 in 1980 to 37 in 1985 and 90 in 1988. The increase in the number of reports in the UK from 1980 to 1982, 1985 and 1988 was 4, 13 and 50 respectively. The total number of reports received in the United States from 1966 to 1984 was 124. The total number of reports received in the UK from 1966 to 1984 was 77. The total number of reports received in Germany from 1966 to 1984 was 54. The total number of reports received in France from 1966 to 1984 was 32.

Agranulocytosis has been reported following administration of amodiaquine in patients with a variety of underlying conditions. The most common factors associated with agranulocytosis due to amodiaquine are listed below:

1. Premedication with other drugs or drugs with a known potential to induce agranulocytosis
2. Concurrent use of anti-malarials with a known potential to induce agranulocytosis
3. Infections, particularly viral infections
4. Hypersensitivity to the drug
5. Immunological factors
6. Genetic factors
7. Drug interactions

The evidence for a causal relationship between amodiaquine and agranulocytosis is supported by the following observations:

1. The agranulocytosis occurs within 1-2 weeks of starting amodiaquine.
2. The agranulocytosis occurs in patients with a pre-existing bone marrow depression.
3. The agranulocytosis occurs in patients with a pre-existing infection.
4. The agranulocytosis occurs in patients with a pre-existing autoimmune disorder.
5. The agranulocytosis occurs in patients with a pre-existing drug allergy.

The mechanism by which amodiaquine induces agranulocytosis is unknown. It is likely that the mechanism is drug induced immune reactions, particularly drug induced immune mediated reactions. The drug is metabolised in the liver and the metabolites are excreted in the urine. The metabolites are thought to be the active components of the drug.

Agranulocytosis is a serious adverse reaction and patients should be monitored closely for signs of agranulocytosis. The drug should be discontinued immediately if agranulocytosis is suspected. The drug should be restarted only after adequate investigations have been carried out.

**References**