

ADVERSE REACTIONS TO RIFAMPICIN WITH SPECIAL REFERENCE TO ACUTE RENAL FAILURE

EDITORIAL

Rifampicin is the most bactericidal drug against mycobacteria, namely *M. tuberculosis* and *M. leprae*.

This drug has been extensively used to treat tuberculosis and leprosy and related side effects are not very frequent according to the available literature.

A few years ago DARLING extensively reviewed this issue using data from treatment of tuberculosis. According to this author, reactions to rifampicin are more severe when this drug is administered intermittently, that is, one, two or three times weekly.

Adverse reactions to daily doses of rifampicin are less common and, if they occur, they are not severe. Most common are the skin reactions and gastric intestinal disturbs, although liver involvement and thrombocytopenic purpura can occur.

Most of the time, skin reactions presents as redness with itching in the face and scalp, including redness and tearing in the eyes. Among gastrointestinal features, we find anorexia, nausea and light abdominal pain and, less commonly, diarrhea. Rifampicin can lead also to liver dysfunction although most of the time they are not severe, mainly in those patients with no previous history of liver damage. There is transient increase in the concentration of serum transaminases and other abnormalities in the liver function tests suggesting a mild alteration in the liverfunction. Thrombocytopenic purpura can occur, with orwithout abnormal bleeding, although it is more frequent during intermittent administration of the drug.

Intermittent administration of rifampicin can lead to all these reactions and also can cause "Flu" Syndrome, dispnea, shock, acute hemolytic

anemia and renal failure.

"Flu" Syndrome consist of fever, shivering, malaise, headache, dizziness and bone pain. The onset is during the 3rd and 6th month of treatment and 1 or 2 hours after drug intake. Isolated episodes of dispnea with orwithout shock can occur, although they are usually associated to the "flu" syndrome.

Acute renal failure can developed as a consequence of acute hemolytic anemia or shock, although these problems are not common. Renal failure can also develop without any unleashing factor. The most commonly renal damage reported is acute tubular necrosis, although interstitial nephritis and cortical necrosis has been also reported. In the literature, there are 50 cases of renal failure with interstitial nephritis related to intermittent rifampicin intake in the treatment of tuberculosis.

In the WHO recommended MDT regimens for leprosy, rifampicin is given monthly in a supervised doses. Although it is an intermittent administration, the period between doses is long enough to avoid occurrence of severe side effects, according to many authors. However, KAR and ROY, in 1984, described a case of multibacillary leprosy that presented acute renal failure in the intake of the 2^o supervised monthly doses of rifampicin. In the next day after taking the drug, the patients presented mild fever, nausea, muscular and joint pain and some unpleasant sensation in the lumbar region. The patient presented also oliguria and, later on, anuria with serum levels of 60mg/100m1 of urea and 4,2 mg/100m1 of creatinine. There was no jaundice or cyanosis. Patient improved after administration of furosemide plus monitorization of hydroelettrolitic balance. While in the hospital,

patient received the 3rd doses of rifampicin and the acute renal failure restarted and subsided after treatment. Rifampicin was then definitely avoided. Authors believe that this is probably the very first case of acute renal failure in a MDT treated patient and they question how frequent should be this complication with the implementation of MDT. They conclude that, although this is a rare complication due to rifampicin, it should be regarded with some concern mainly in relation to those patients treated in field conditions.

In 1986, DEDHIA et alii. described another case. refers to a patients with hypochromic patches that initially received dapsone and than 600 mg of rifampicin once a week. After the 13rd doses presented fever, muscular pain and articular pain. While taking the next two doses he again showed the same symptoms. Afterwhile, rifampicin was discontinued and symptoms disappeared. Later one, rifampicin was given monthly (600 mg) and the patient presented severe fever, muscular pain, abdominal pain, vomiting, dizziness, articular pain and, afterwards, oliguria with high levels of urea and creatinine. Patient improved its condition after hemodialysis. Renal biopsy showed acute interstitial nephritis with infiltration of monocytes and eosinophils.

PALANDE, in 1990, while describing the toxicity of rifampicin, mention a severe complication, although rare, that start to be recognized in the course of leprosy treatment. He talks about oliguria due to tubular necrosis or interstitial nephritis and considers that they are probably due to immunological mechanisms since, in these cases of nephritis, anti-rifampicin antibodies have been frequently demonstrated in the blood. He mention 3 of such cases fully recovered with hemodialysis.

GUPTA et al. refers two other cases. One of them, a borderline tuberculoid case, started treatment with dapsone 100mg/daily, clofazimine 200mg/daily and rifampicin 600mg/monthly. After 3 hours of intake of the 8'h monthly doses of rifampicin, he presented fever, malaise, shivering, lumbar pain, nausea, vomiting and, later on, anuria. Clinical examination revealed pale skin, jaundice, acidotic breath and sleepy. Laboratory finding revealed severe intravascular hemolysis, hypercalcemia and renal failure. Renal biopsy showed acute tubular necrosis with pigment casts

in the tubules. After dialysis the patient improved. Unaware of its condition, patients took rifampicin again and after 30 minutes the initial condition repeated.

The second case, probably a borderline patient, did not used WHO recommended MDT. Started treatment with dapsone 100mg/daily and, later on, 600 mg of rifampicin was added each two weeks. Four months later, after taking the rifampicin doses he presented dispnea, vomiting, diarrhea and, later on, generalized edema. Clinical and laboratory examination showed a pale skin, edema and high levels of urea and creatinine (210mg/dl and 13,4mg/dl respectively) and the renal biopsy revealed acute tubular necrosis with pigment casts in some tubules. Patient improved after dialysis.

In February 1992 there was 1.295.640 patients under MDT in the world and 2.870.944 - cases released from treatment. Taking in account the number of published cases of complications, the risk of adverse reactions with this therapeutic regimen is very low, moreover with reference to rifampicin and particularly with reference to acute renal failure due to its intermittent administration (once monthly).

For this reason, facts that have been reported in Brazil call our attention to this issue.

MDT was introduced in Brazil in 1986 and its implementation is slow but steady. In the end of 1992 there was 23.81% of the 250.066 registered cases under MDT. This is fairly low as regards the number of cases in other endemic countries with similar epidemiological conditions. Even though, at least 12 cases of renal failure due to rifampicin have been reported in some state of Brazil, including some with death as final outcome. After careful examination of the medical records of some of these patients, we could not assure that the symptoms were due to rifampicin, although in other cases there was a net correlation.

Unfortunately, all these cases in Brazil were not published. For this reason, we strongly recommend an article regarding this question published in this issue.

In São Paulo State, some of these cases posed problems to the continuing implementation of MDT. Some health units showed a great concern in continuing to use WHO/MDT. This is quite

understandable, since it is strongly disturbing to doctors to have a patient presenting acute renal failure after 2 hours of drug intake, sometimes leading to death, including the fact that most of these health units have no or little possibilities to immediately refer these cases for adequate management of the complication in a specialized hospital.

For this reason the Leprosy Control Program and the Center of Epidemiology of São Paulo Health Secretariat developed a special form for notification of adverse reactions related to MDT. This form includes identification of the patient and data related to the treatment, exams previous to commencement of treatment, allergic reactions to other drugs, other diseases, signs and symptoms related to suspected side effects, clinical and laboratory exams made and treatment prescribed in this situation.

The outcome of this study will be of utmost importance to correctly quantify and qualify side effects related to WHO/MDT, since the majority of reports on these aspects showed to be related not to problems with the drugs itself but to reactional episodes or other interferences due to the disease as a whole.

However, the number of reported cases of acute renal failure due to monthly doses of rifampicin in Brazil is sums to be impropotion greater than in other countries in the world where the number of patients treated with MDT is higher. As a matter of fact, there are few of these cases in the international literature what is supported by personal reports of experienced doctors working with MDT. Thus, we can concluded that these cases are indeed very rare in the rest of the world. Why would they occur more frequently in Brazil? Would it be for racial or geographical differences making our patients more prone to develop ad

verse reaction and acute renal failure? This seems not to be probable since the number of cases is too small to arrive to this conclusion. Perhaps, the reason lies in the difference of development of the control programmes. In Brazil, in the majority of its states, the treatment of leprosy patients is made by specialized doctors who have more conditions to detect such severe adverse effects. In other countries the major part of this job lays on paramedical workers who, to some extent, do not have enough experience to recognize most of the side effects of the MDT drugs. It is also true that in the Amazonas regions, where most of the work is done by paramedicals, there was one reported case of acute renal failure, but this happened in Manaus, in a reference center. One can argue how many similar cases could have occurred with patients living along the rivers which are usually visited only by paramedical workers? Probably many of these adverse effects are misdiagnosed as many other diseases that afflicts man in the amazonia region.

Although rare, acute renal failure due to the monthly doses of rifampicin is severe and sometimes fatal. For this reason, health personnel and patients should be aware of this possibility. As suggested by PALANDE, patients should remain in the health unit for a couple of hours after taking rifampicin capsules and should be clearly warned to immediately return to the health unit if he/she feels some strange symptoms until the next day of the monthly pulse of rifampicin.

However, all these facts should not be regarded as an obstacle to the use or implementation of WHO/MDT due to the overwhelming benefits of this regimen in the fight against leprosy.

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