# Letter to the Editor

## Potential utility of indomethacin in enhancing the leishmanicidal activity of glucantime

The trypanothione biosynthetic pathway is common to the trypanosomatid family of protozoa, which includes *Leishmania* and *Trypanosoma* spp. and is absent in the host systems. This pathway constitutes an important target for chemotherapy against leishmaniasis.

The trypanothione pathway combines 2 metabolic pathways: the polyamine biosynthetic pathway and the glutathione pathway. Since glutathione (GSH) is involved in a number of vital functions within cells, chiefly defence against oxidative damage, GSH inhibition is a potential means for chemotherapy against these parasites [*1*].

Moreover, GSH depletion in macrophages leads to increased nitric oxide production, which has leishmanicidal action. In this way, it has been shown that buthionine sulfoximine, an inhibitor of GSH synthesis, exerts an inhibitory effect on *L. donovani* growth [*1*]. On the other hand, resistance of *L. donovani* to sodium stibogluconate is related to the expression of host and parasite gamma-glutamylcysteine synthetase, which produces GSH [*2*]. Resistance of *L. major* and *L. tropica* to glucantime was also attributed to higher GSH levels [*3*].

Indomethacin is known to decrease cellular GSH levels [*4*]. Through this mechanism, it enhances the effect of chloroquine against malaria, which, like *Leishmania*, is an intracellular parasite [*4*]. Indomethacin treatment slows disease progression and enhances a type 1 helper (Th1) cell response in susceptible BALB/c mice infected with *L. major* [*5*].

*In vitro* indomethacin administration upregulates interleukin-12 production and polarizes the immune response towards a Th1 type in susceptible BALB/c mice infected with *L. mexicana* [*6*]. Combined treatment with interleukin-12 and indomethacin promotes increased resistance in BALB/c mice with established *L. major* infections [*7*]. Theses effects can be explained by the observations that, first, prostaglandins may play a role in the loss of interleukin-12 responsiveness observed during nonhealing of *L. major* infections [*5*] and, secondly, that prostaglandins can inhibit the development of Th1 response and enhance the development of type 2 helper (Th2) cell response [*7*].

Given the above facts, indomethacin, especially in the topical form, may prove to enhance the antileishmanial activity of glucantime. Clinical trials on this subject are warranted.

### *References*

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