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].

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 up-regulates 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**


2. Carter KC et al. Resistance of *Leishmania donovani* to sodium stibogluconate is related to the expression of host and parasite gamma-glutamylcysteine synthetase.


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