Haptoglobin Phenotypes: Chloroquine and halofantrine induce a state of ahaptoglobinemia in patients receiving either drug for treatment

Quaye IKE, Ekuban FA, Gyan BA, Cornelius D
Clinical Pathology Unit, NMIMR, PO Box LG 581, Legon, Ghana

Changes in haptoglobin phenotypes were determined by polyacrylamide gel electrophoresis on serum samples from patients infected with plasmodium falciparum malaria, and who were receiving treatment with chloroquine or halofantrine.

Serum samples from the treatment groups were obtained on day 1 (before drug treatment), 2/4, 7 and 28 depending on whether halofantrine or chloroquine was administered. We observed that in patients determined as having either Hp2-1 or Hp2-2 phenotype, the expression of haptoglobin was inhibited partially or completely on day 7 following halofantrine treatment. The normal expression of the phenotype was however restored on day 28 following treatment. In contrast, inhibition of the expression of the phenotypes in patients taking chloroquine was seen immediately following chloroquine treatment. The normal expression was however not restored at the end of the 28 day sampling period.

The results indicate that drug related inhibition of haptoglobin expression may contribute to a state of ahaptoglobinemia. This inhibition is severe under the influence of chloroquine than halofantrine.

PERMEABILITY OF ORAL MUCOSAL TISSUES TO DEX-AMETHASONE

Oral Diseases Research Centre, St.Bartolomew’s & the Royal London School of Medicine & Dentistry, and *IRC in Biomedical Materials, Queen Mary & Westfield College, London, E1 2AD, U.K.

Topical steroids are used to treat chronic inflammatory lesions of the oral mucosa, but this treatment is often ineffective. As part of a study to improve topical mucosal steroid delivery, this study aimed to analyse the barrier properties of normal mucosa to the synthetic steroid, dexamethasone (DEX).

The permeability of 3H-DEX in vitro, across porcine buccal mucosa, hard palate and ventral tongue, was assessed using a continuous Flow Chamber system and the permeation constant (Kp) calculated. The amount of DEX present within each tissue was measured following solubilisation with 1M NaOH, and the 'systemic' delivery calculated from the total cumulative amount delivered across the mucosa. In addition, the tissue was exposed to FITC-DEX and visualised by fluorescence microscopy.

There was a steady increase in permeability over time for all sites. The amount of steroid remaining within the tissue ranged from 5% in hard palate to 7% in buccal mucosa over 18 hours. In contrast, less than 1% of the drug was delivered systemically across the mucosa. FITC-DEX revealed a regional variation in uptake. Buccal mucosa and ventral tongue were relatively permeable with evidence of labelled steroid in the lower layers of the epithelium within 1 hour. For hard palate, this penetration was limited to the superficial layers. The low 'systemic' delivery of DEX compared to the amount retained may be the result of the tissue acting as a reservoir for the drug. This is supported by the examination of the tissue after exposure to FITC-DEX. This may help explain the low incidence of systemic side effects, and the relatively poor efficacy associated with the administration of topical steroids to oral mucosal tissues.

Intracellular stability of antisense oligonucleotides protected by the (d(GCGAAGC)) hairpin

T. Djavanbakht, B. Jolles, A. Laigle
LPBC (CNRS ESA 7033), Université P & Marie Curie, Paris, France

Antisense oligodeoxyribonucleotides (ODNs) can be protected against enzymatic attack of serum, mostly due to 3'-exonucleases, by addition at their 3'-end of the sequence d(GCGAAGC) which spontaneously forms a hairpin which is known for its extraordinary stability with regard to thermal denaturation or nuclease degradation. This hairpin structure does not prevent hybridization of the 5'-stem part of the antisense ODN and can itself contribute to hybridization. The question of the protective effect of the hairpin once the ODs are inside the cells remained opened. It has been checked in K562 and 3T3 cell lyses. Kinetics of degradation of ODs protected or not by the hairpin have been compared to that of a phosphorothioate ODN by a FRET (Fluorescence Resonance Energy Transfer) method. In that purpose, ODs have been labeled with rhodamine on their 5'-end and fluorescein on their 3'-end. Since the fluorescence spectrum of fluorescein overlaps with the absorbance spectrum of rhodamine, the excitation of fluorescein induces fluorescence of rhodamine while its own fluorescence decreases - this is the FRET process. The FRET decrease allowed (i) to demonstrate that the hairpin actually protects the ODN inside the cell; (ii) to compare this protection with that already demonstrated in the serum, (iii) to evidence different enzymatic composition of lysates of different cell strains. PAGE electrophoresis of 32P labelled ODN is informative about the type of nucleasic attack undergone by the ODs.