- Abstract

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A quantitative assessment of protoporphyrin IX metabolism and phototoxicity in human skin following dose-controlled delivery of the prodrugs 5-aminolaevulinic acid and 5-aminolaevulinic acid-n-pentylester.

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Abstract

BACKGROUND:
Topical 5-aminolaevulinic acid (ALA) is widely used in photodynamic therapy (PDT) to generate protoporphyrin IX (PpIX) in the skin. However, other prodrugs may be more effective.

OBJECTIVES:
The pharmacokinetics of ALA- and ALA-n-pentylester-induced PpIX, together with the phototoxicity after PDT, were compared in human skin in vivo, using iontophoresis as a quantitative drug delivery system.

METHODS:
A series of six increasing doses of equimolar prodrug solutions was iontophoresed into normal skin of the upper inner arms of 20 healthy subjects. The kinetics of PpIX metabolism in skin (n = 4) and the response to light exposure, performed at 4.5 h (n = 6) and 6 h (n = 10) after application, were assessed by skin surface PpIX fluorescence and postirradiation erythema.

RESULTS:
ALA and ALA-n-pentylester showed a linear correlation between logarithm of dose and PpIX fluorescence ($P < 0.005$), and logarithm of dose and skin phototoxicity with irradiation at 4.5 h ($P < 0.001$ and $P < 0.005$, respectively) and 6 h ($P < 0.05$ and $P < 0.0001$, respectively) after iontophoresis. Higher phototoxicity was observed with ALA-n-pentylester than with ALA when sites were irradiated at 6 h, as indicated by the significantly lower theoretical threshold dose for erythema ($P < 0.05$) and the shift of the PpIX fluorescence/phototoxicity curve towards greater skin erythema at equal PpIX fluorescence levels. Depth of PpIX fluorescence in skin, as determined by fluorescence microscopy, was similar for both prodrugs, but a more homogeneous distribution of PpIX was seen with the more lipophilic ALA-n-pentylester.

CONCLUSIONS:
The observed greater phototoxicity of ALA-n-pentylester relative to ALA may be attributable to a more favourable PpIX localization in tissue and/or greater intrinsic toxicity.

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