COMMENTARY

Degradation and Metabolism of Mometasone Furoate in Humans: Influence of Reversible, Sequential Metabolism, and Ionic Strength

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Recently, Valotis et al.[1] published a study on human receptor kinetics, tissue binding affinity, and stability of mometasone furoate. They reported some novel and insightful data on human receptor kinetics demonstrating fast and extensive association to the human glucocorticoid receptor with dissociation of the mometasone furoate receptor complex faster than fluticasone propionate. This is an important finding as the tissue affinity of inhaled mometasone furoate and the redistribution from lung tissue into systemic circulation is a determinant of pharmacological action.

However, Valotis et al.[1] reported "there has been no information about the stability of mometasone furoate in human lung tissue or human plasma." The authors state "so far, there has been no published data on the stability of mometasone furoate in the therapeutic target tissue, for example, human lung." Furthermore, it is not clear yet which degradation products are formed in human plasma. Valotis et al.[1] give reference to some of our published work.[2–4] In these studies, we detected and published the presence of four degradation products of mometasone furoate in human plasma in a validated HPLC method.[2] Valotis et al.[1] developed an alternative and more sensitive method of HPLC analysis, however, no information is available as to whether this assay was validated for precision, accuracy, and recovery, acording to Food and Drug Administration Guidelines. We further examined the degradation kinetics in aqueous systems and demonstrated that there was a pH-dependent and also ionic strength dependent degradation.[3] Furthermore, we characterized the degradation and metabolism of mometasone furoate in rat tissues and fluids.[4] In doing so, we examined each preparatively isolated degradation product formed and their sequential degradation pathways.

In the article of Valotis et al.,[1] the "open questions" concerning receptor binding kinetics, tissue affinity, and stability of mometasone in human lung tissue and plasma were addressed. The stability of mometasone furoate in human lung tissue and plasma was published and presented at international pharmaceutical conferences in 1999–2000[5–7] and again in 2002[8–10] by our laboratory. Indeed, our initial article[2] also provided kinetic stability data in human plasma, and demonstrated additional degradation products characterized in follow up articles.[2–4] A study detailing mometasone furoate degradation and metabolism in human biological fluids and tissues including kinetics was published by our laboratory in 2003.[11]

We have demonstrated that degradation of mometasone furoate in S1 and S-9 fractions of human lung tissue was qualitatively and quantitatively comparable.[10,11] Mometasone furoate

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decomposed slowly in human lung S-9 fraction. Following the incubation of mometasone furoate ($C_0 = 19.2$ μM) at 37°C for 72 h, the formation of the 9β,11β-epoxide (A) was a major pathway while the C-17 side-chain dehydration and rearrangement were two minor routes yielding 9α,21β-dichloro-11β,21α-dihydroxy-16α-methylpregna-1,4,17,20-tetraen-3-one 21-(2-furoate) (B), and 21β-chloro-21α-hydroxy-16α-methyl-9β,11β-oxidopregna-1,4,17,20-tetraen-3-one21-(2-furoate) (C), respectively. In human plasma products B and C were formed in appreciable amounts dependent on incubation time. Another product 21-chloro-17α-hydroxy-16α-methyl-9β,11β-oxidopregna-1,4-diene-3,20-dione (D) the hydrolyzed form of the 9β,11β-epoxide was not detected in S-9 fractions of human lung during 72 h incubation and barely detectable in human plasma. Hydrolysis of the C-17 furoate moiety of the drug was also not observed in human lung *in vitro*. Similar observations have been previously reported for some other C-17 esterified glucocorticoids, such as budesonide and beclomethasone dipropionate, in which hydrolysis of the C-17 ester bond is not significant in human lung, human serum or plasma *in vitro*.[12,13] These obervations are in accordance with the previous finding that hydrolysis of steroidal esters is dependent on the position and the chemical properties of the ester-bond. These results again suggest little involvement of esterase(s) in the degradation of mometasone furoate in human lung.[11]

Either with or without cofactors there was no 6β-hydroxyl or other oxidative and reductive products of mometasone furoate detected during the incubation in S-9 fractions of human lung tissue from any subject. This is in agreement with the finding by Zbaida et al.,[14] who has reported that mometasone furoate is not metabolized by lung microsomes from rat, mouse, dog, and human. According to a metabolism study using chemical inhibitors *in vitro*, the Phase 1 oxidation reaction of 6β- hydroxylation of mometasone furaote was mainly catalyzed by rat CYP3A in rat liver and intestinal microsomes.[4] The negligible 6β-hydroxylation of mometasone furoate in human could result from the low expression of drug metabolizing enzymes, including CYP3A, in human lung.[15]

On the other hand, the addition of cofactors significantly inhibited the decomposition of mometasone furoate in S-9 fraction of human lung tissue. The cofactors, including $MgCl_2$, an NADPH-generating system and molecular oxygen (in the form of 95% oxygen and 5% carbon dioxide), are necessary for maximizing activity of monooxygenase enzymes. Due to the very low enzyme activities in human lung, addition of cofactors would not facilitate the metabolism of mometasone furoate but increase the ionic strength of the incubation mixture (by 0.03). The latter has the potential to reduce the decomposition of this drug as previously demonstrated.[3]

Valotis et al.[1] suggest that suprisingly little precise information is available on . . . "formation . . . or degradadation products in humans." In addition, "no additional degradation products were identified under the chosen chromatographic conditions." Our results under different chromatographic conditions and after preparatively isolating each degradation product and examining their individual stability demonstrate that other degradation products are possible in human tissues and fluids.[2,5–11] Valotis et al.[1] assert that "it must be assumed that 9,11-epoxy mometasone furoate was subject to follow-up reactions" this is in accordance with what we have previously demonstrated.[2,5–11] Importantly, the 9,11 MF epoxide has previously been reported to be converted to mometasone furoate with hydrogen chloride gas in dichloromethane or with concentrated HCl in acetic acid.[16,17] Thus, the conversion between mometasone furoate and the 9,11-MF epoxide appears to be reversible under certain conditions and the direction of the reaction may be governed by hydrogen and chloride ion as well as pH. This may explain the lack of degradation in buffer solution pH 5.4[1] and previous pH-depedency findings.[3]

Interestingly, D and mometasone (M), the hydrolysed forms of 9,11-MF expoxide and mometasone furoate respectively, were not detectable in lung tissues from any subject. It is suggested by Valotis et al.[1] that "the 6-OH MF, a metabolite is most probably generated in the liver."[1] It is important to note that human intestinal microsomes can also produce the 6-OH MF metabolite.[11] In the the lung this metabolite has the *ab initio* potential but limitied capacity to form, as the metabolite concentrations in the lung fell below our detectable concentration range in our studies.[11]

In pooled human plasma of pH 7.18 at 37°C, the decomposition profile of mometasone furoate ($C_0 = 19.2$ μM,) demonstrated a half-life of mometasone furoate of 18.4 ± 4.3 h.[11] Interestingly, significantly higher amounts of B were observed in human plasma compared to lung tissues.[11] These results indicate that the degradation reactions of mometasone furoate are further

catalyzed by some unknown component in human plasma.

Overall our data in human tissues agrees with the findings of pH-dependent formation of mometasone furoate 9,11-epoxide, and instability of mometasone furoate in human lung tissue and plasma.[11] Valotis et al.[1] have identified the same major degradation product and found similar adsorption to tissue as we have demonstrated. Recently, novel insights into the degradation process with similar degradation products and confirmatory mass spectral data have been published. Condensation between the furoate ester carbonyl and the methylene group at C21 leads to the formation of a cyclized five membered ring and the product 21-Chloro-22-(furan-2-yl)-9, 11-epoxy-16-methyl-23-oxa-[13,14,15,16,17,17,20,21,22,23]spiro[4,4]-pregna-1,4,21-triene-3,20-dione.[18] It remains possible that other parallel and subsequent degradation and metabolism pathways could also be involved.[10,11] The differences in rates of degradation between different studies might be due to different experimental settings (e.g., lung tissue pieces versus lung microsome fractions, different buffer concentrations, and differences in buffer ionic strength and in method of analysis).

It is also important to recognize that the 9,11-MF epoxide and the 6-β hydroxy mometasone furoate have comparable binding affinities to the glucocorticoid receptor of rat skin tissue.[19] The binding affinities of the metabolite 6β hydroxyl mometasone furoate and the degradation product 9,11 epoxy mometasone furoate to the human glucocorticoid receptor is twice as high as dexamethasone and similar to the activity of the corticosteroids flunisolide and triamcinolone acetanonide.[20] It is entirely possible that the other degradation products we have identified and other metabolites have clinical activity if they have similar binding affinities in humans. Thus, we agree that "a clinical trial measuring the mometasone furoate parent compound as well as metabolites and degradation products is necessary"[1] given the, the interesting observations generated in the article by Valotis et al.[1] and Sahasranaman et al.[18] and our conclusions from previously published human data on the degradation and metabolism pathways of mometasone furoate.[11]

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