Highlights of a publication comparing the systemic bioavailability of topical diclofenac sodium gel 1% with oral diclofenac sodium tablets

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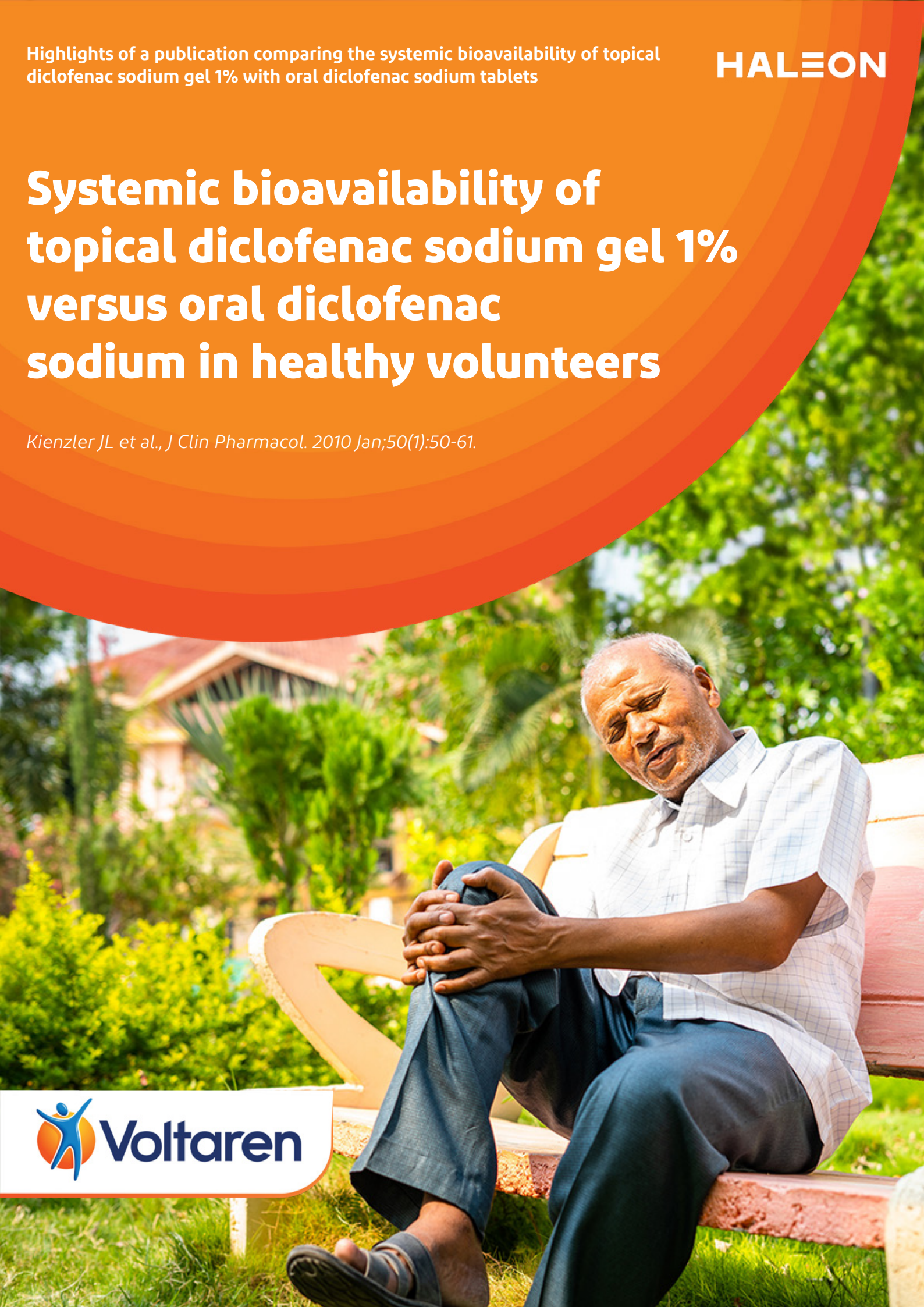
Systemic bioavailability of topical diclofenac sodium gel 1% versus oral diclofenac sodium in healthy volunteers

Kienzler JL et al., J Clin Pharmacol. 2010 Jan;50(1):50-61.



Voltaren

Background and Objective

- Oral nonsteroidal anti-inflammatory drugs (NSAIDs) are a preferred therapy for osteoarthritis (OA) because they effectively relieve pain and reduce inflammation
- However, long-term use of oral NSAIDs can be associated with renal, gastrointestinal, and cardiovascular complications
- Topical NSAIDs represent a potential alternative to oral NSAIDs offering comparable efficacy via similar mechanism of action following local administration with less systemic exposure
- Diclofenac sodium gel (DSG) 1% is the first topical NSAID approved for use in the United States for the relief of pain of osteoarthritis (OA) joints, such as the knees and of the hands

Objective: To compare the systemic bioavailability and pharmacodynamics of topical diclofenac sodium gel 1% vs. oral diclofenac sodium 50-mg tablets

Study Design and Methodology

Seven-week, single-center, randomized, open-label, multiple-dose, 3-way crossover study conducted in healthy volunteers ≥ 50 years (n=40). To approximate the general OA population, at least half of all participants were aged ≥60 years and 50% to 70% were women.

Treatment arms

Diclofenac sodium gel 1%, 16g/D, (DSG 16g/D)

4 g of DSG 1% applied to 1 knee, 4X daily for 7 days

Diclofenac sodium gel 1%, 48g/D (DSG 48g/D)

12 g of DSG 1% applied to both knees and hand 4X daily for 7 days

Diclofenac sodium 50-mg tablets, 150 mg/D (DS Tab)

Oral diclofenac 50 mg taken 3X daily for 7 days

Endpoints

Pharmacokinetic

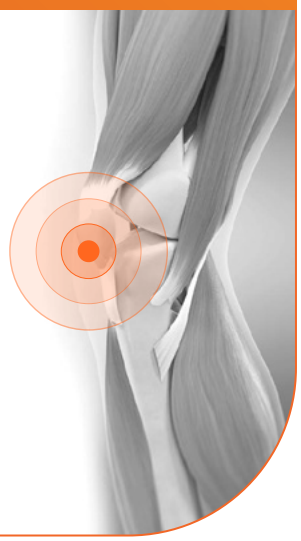
- All pharmacokinetics parameters measuring systemic exposure i.e. AUC_{0-24}, and C_{max}, Ae_{0-24} of diclofenac and its hydroxylated metabolite and peak-trough fluctuation (i.e., C_{max}-C_{min}/C_{av})

Pharmacodynamic

- Inhibition of COX-1, COX-2, and platelet aggregation

Safety

- Incidence rates of treatment-related AEs, changes in physical findings and vital signs

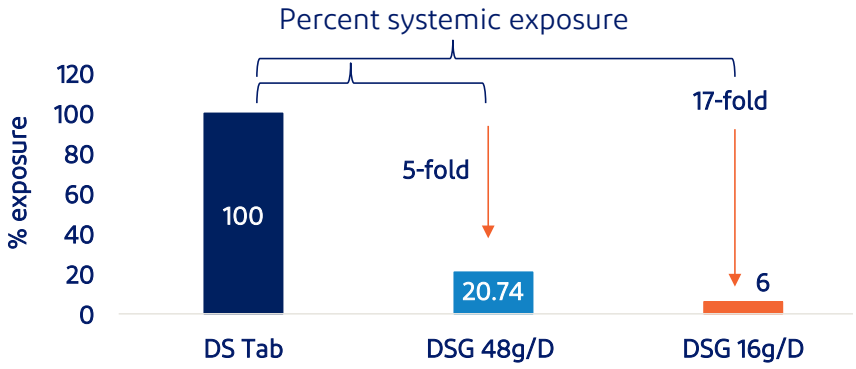


Abbreviations: AEs = Adverse events; COX = cyclooxygenase; DSG = Diclofenac sodium gel; DS Tab = Diclofenac sodium tablet; AUC_{0-24} = Area under the plasma concentration versus time curve from 0 to 24 hours; Ae_{0-24} = total urinary excretion over 24 hours; C_{max} = maximum plasma concentrations; C_{min} = minimum plasma concentrations; C_{av} = average plasma concentrations

Results

Pharmacokinetics

Systemic exposure and maximum plasma concentrations of diclofenac were significantly lower with DSG than with DS Tab



- The AUC_{0-24} for DS Tab was ~17-fold higher than for DSG 16g/D and ~5-fold higher than for DSG 48g/D
- C_{max} for DS Tab was approximately 150-fold higher than for DSG 16g/D and 40-fold higher than for DSG 48g/D

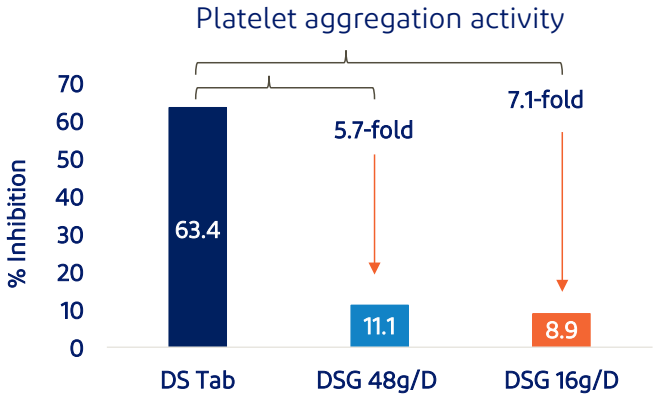
- Peak in plasma concentrations were seen ~1 hour after each administration of DS Tab, however, no obvious peaks in absorption related to topical DSG 1% application were observed
- Total urinary excretion of diclofenac and its hydroxylated metabolite were consistent with the corresponding ratios for AUC_{0-24} and C_{max} for DSG compared with DS Tab

What does it mean?

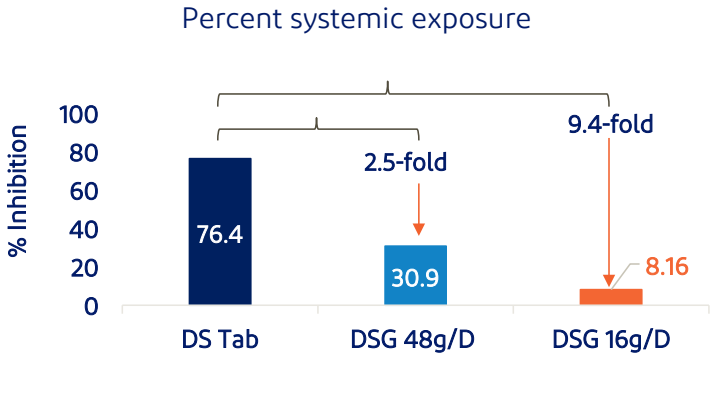
- Reduced systemic exposure with topical diclofenac translates to improved tolerability due to less likelihood of systemic AEs related to gastrointestinal, cardiovascular and renal system

Pharmacodynamics

Platelet aggregation and COX-1 were minimally inhibited by DSG when compared with DS Tab



- Inhibition with DS Tab was 7.1-fold higher than for DSG 16g/D and 5.7-fold higher than for DSG 48g/D ($p<0.001$ for both)



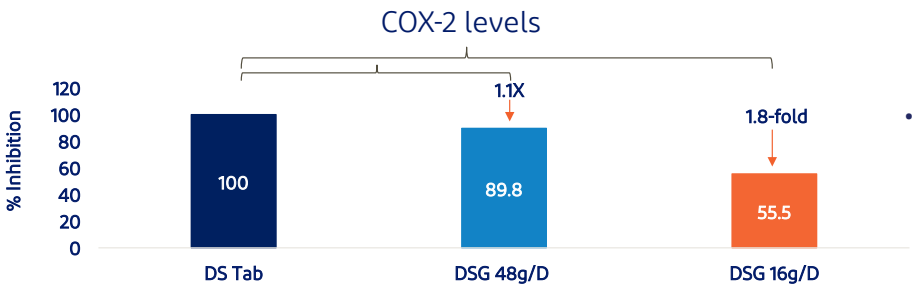
- Inhibition with DS Tab was 9.4-fold higher than for DSG 16g/D and 2.5-fold higher than for DSG 48g/D ($p<0.001$ for both)

What does it mean?

- Normal platelet aggregation activity is essential in maintaining cardiovascular (CV) health. Therefore, minimal inhibition of the activity by topical diclofenac ensures low risk of CV-related AEs
- COX-1 are constitutive enzymes that mediate protective physiological functions in most tissues, such as gastrointestinal mucosa and kidney. Thus, low level of inhibition of COX-1 by topical diclofenac ensures minimal risk of gastrointestinal or renal injury

Abbreviations: AEs: Adverse events; AUC_{0-24} : Area under the plasma concentration versus time curve from 0 to 24 hours; Ae_{0-24} : total urinary excretion over 24 hours; C_{max}: maximum plasma concentrations; COX: cyclooxygenase

COX-2 was suppressed considerably by DSG, even at the lower diclofenac doses



- Inhibition with DS Tab was comparable to DSG 48g/D and 1.8-fold higher than for DSG 16g/D

What does it mean?

- COX-2 are enzymes that are induced during inflammation but are present at low levels under normal conditions. Therefore, inhibition of COX-2 by topical diclofenac is essential to achieve relief from inflammation and pain

Safety

Rates of AEs were comparable between topical and oral diclofenac; however, only oral form was associated with gastrointestinal AEs

- **7 participants** experienced an AE considered to be potentially related to the treatment

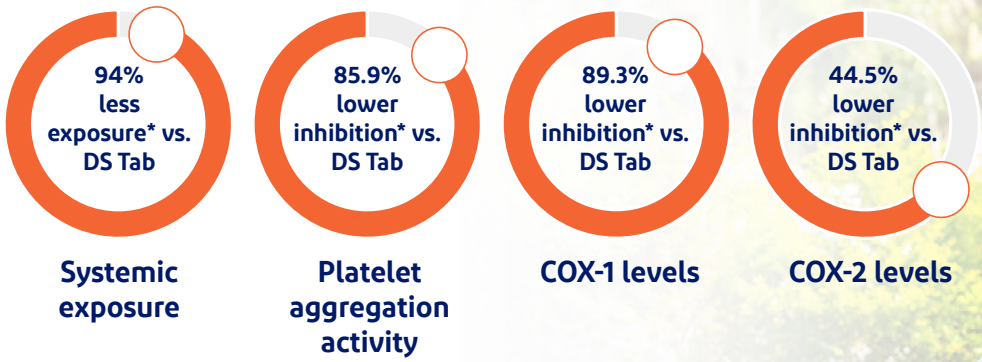
Topical Diclofenac (n=4)

Restricted to localized reactions, such as dermatitis, erythema, pruritus, and paresthesia in both knees

Oral Diclofenac (n=3)

Gastrointestinal disorders, including eructation, dyspepsia, and abdominal pain

Diclofenac gel is comparatively well-tolerated option for pain management than oral diclofenac tablets



Conclusion

- DSG 1% shows significantly lower systemic exposure and fluctuation in plasma levels compared with oral diclofenac sodium
- Topical formulation causes significantly lower inhibition of platelet aggregation and COX-1 levels and considerable suppression of COX-2 levels when compared with oral diclofenac
- Topical diclofenac, with a more favorable safety profile, represents a useful alternative to oral diclofenac therapy in pain management

Abbreviations: AEs: Adverse events; AUC_{0-24} : Area under the plasma concentration versus time curve from 0 to 24 hours; Ae_{0-24} : total urinary excretion over 24 hours; C_{max}: maximum plasma concentrations; COX: cyclooxygenase