Human Skin Absorption and Penetration Study of Four Different Topical Formulations of 5-Fluorouracil

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Synopsis

- Cunningham et al[1] compared the efficacy and tolerability of 5% 5-fluorouracil (FU) cream + 0.005% calcipotriol ointment combination (FU+C) with FU + vaseline combination (FU+V) treatment of actinic keratosis (AKs).
- The FU+V control resulted in 0% of participants having complete clearance of face AKs and an unexpectedly low 4% of participants developing severe erythema, possibly due to vaseline interfering with FU absorption.
- Mohney et al[2] concluded that petrolatum + 5-FU is an inappropriate control and no superiority claims from that study can be made vs topical FU.
- We report a 20-fold reduced penetration of FU in the presence of vaseline (FU+V), and a 73% reduction in FU penetration in the presence of calcipotriol ointment (FU+C).

Objective

- To compare the skin absorption/penetration of 4 different 5% 5-FU formulations, including FU+V.

Methods

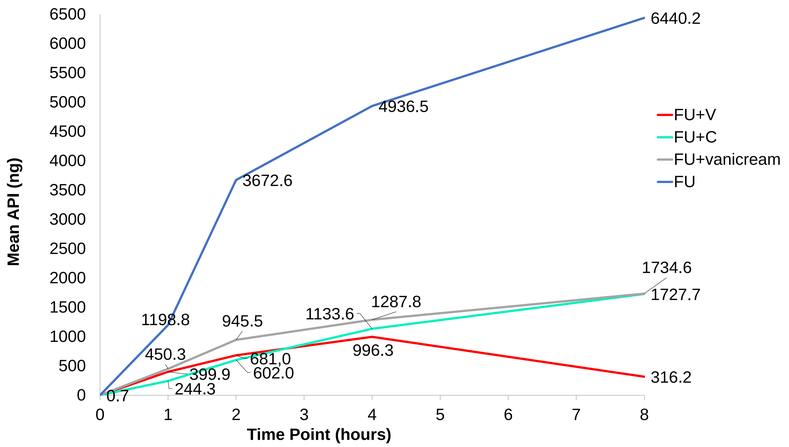
- This is a mass balance study comparing marketed 5-FU alone (FU) and 1:1 weight combinations in vaseline (FU+V), 0.005% calcipotriol ointment (FU+C) and vanicream (FU+vanicream).
- *In vitro* percutaneous absorption and penetration through dermatomed human cadaver skin were assessed. After passing initial visual inspection, barrier integrity of the skin tissue was evaluated using transepidermal electrical resistance measurement. Skin permeation (5-6 specimens for each test preparation) into receptor medium was studied at a clinically relevant 8 hours.

Results

- At 8 hours, the mean (standard error of the mean) amount of FU penetrating into the receptor medium was 6,440.2 (1,943.2) ng for FU alone, 316.2 (162.1) ng for FU+V, 1,727.7 (603.4) ng for FU+C and 1,734.6 (542.3) ng for FU+vanicream (**Fig. 1**).
- The percentage release amount of FU in receptor at 8 hours was 1.1%, 1.7%, 1.3% and 5.0% and the percentage of FU in the total absorbed dose was 10.1%, 9.2%, 7.3% and 18.7%, respectively (**Fig. 2**).
- The concentrations of FU in the receptor at 8 hours are shown in **Fig. 3**.

Results

Figure 1. Mean Amount of 5-Fluorouracil in Receptor from 0 to 8h



API, active pharmaceutical ingredient; FU, 5% 5-FU cream alone; FU+V, FU+ 1:1 weight combinations in vaseline; FU+C, FU+ 1:1 weight combinations 0.005% calcipotriol ointment; FU-vanicream; FU+ 1:1 weight combinations vanicream

Figure 2. Percentage Release Amount of 5-Fluorouracil in Receptor from 0 to 8h

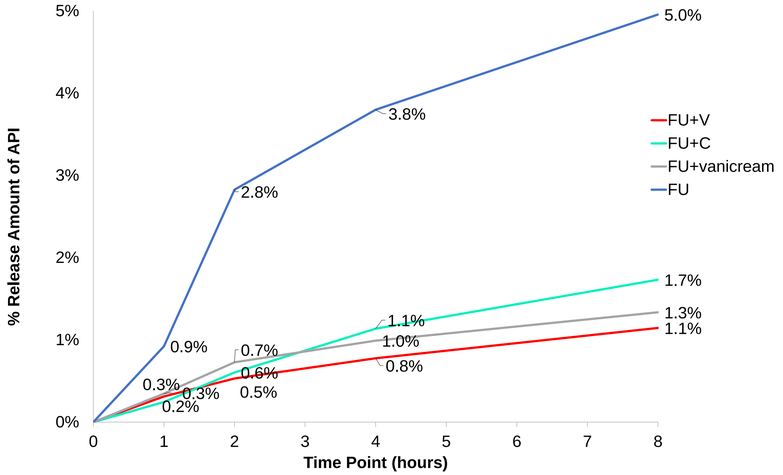


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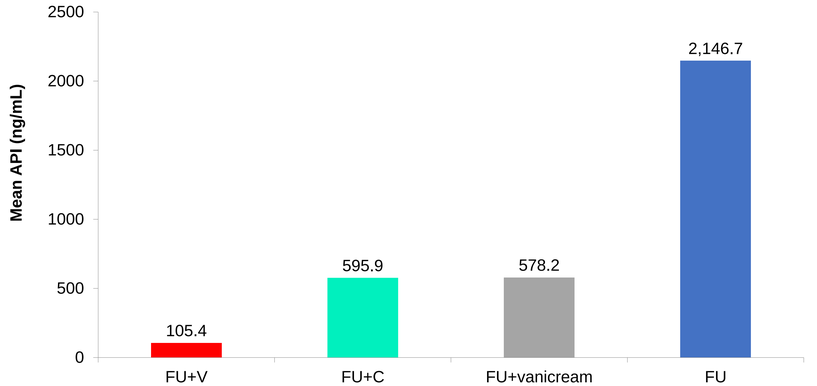
Figure 3. Mean 5-Fluorouracil Concentration in Total Absorbed Dose at 8h



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Conclusions

- Combining 5% 5-FU cream with vaseline interfered with the FU penetration through skin, which was 20-fold lower with FU+V than with FU.
- This degree of reduction in penetration is greater than simply explained by the lower final FU concentration in FU+V applied (2.5%).
- This markedly reduced penetration of FU in the presence of vaseline (FU+V), taken with the 73% reduction in FU penetration in the presence of calcipotriol ointment (FU+C), further point to the inappropriateness of using a FU+V combination as a control for clinical studies and could lead to erroneous superiority claims.

References

- [1]Cunningham et al. J Clin Invest. 2017; 127:106-116.
- [2] Mohney et al. J Drugs Dermatol. 2022;21:60-65

Acknowledgements

- Writing assistance provided by TFS HealthScience.
- This study was funded by Almirall.

Conflicts of interest

- BB received consulting honoraria from Almirall, Biofrontera, BMS, Pfizer, Evommune, Aiviva, Sirnaomics, Pulse and Mediwound;
- PT is an Almirall USA employee.

Fall Clinical Dermatology Conference, Las Vegas, 20-23 October 2022