The power of science:

Research leads to change in generic-substitution law

When filling a prescription, a generic is most often dispensed due to the generic-substitution law. However, generics are allowed to contain different additives than the branded drug, including the preservative. Recently, the Danish Medicines Agency changed the legislation to state that generics must contain the same preservative as the branded drug. Researchers joined forces with Fight for Sight, Denmark, and this continuous dialogue led to the legislation change.

The generic-substitution law

According to the European Medicines Agency, a prescribed branded drug can be substituted with a generic drug because they are considered identical to the branded drug regarding safety and efficacy. The active pharmaceutical ingredient, dispensation form, and indication must be the same for branded and generic preparations.[1] The efficacy and safety studies performed on the branded drug are, therefore, considered applicable to the generic drug as well. However, inactive ingredients may vary. This includes preservatives. For example, until recently, the branded travoprost eye drop Travatan® contained the preservative Polyquad®, whereas the generic alternatives contained benzalkonium chloride (BAK). For a Travatan prescription, an eye drop with BAK may thus be dispensed. Because the pharmacy is required to dispense the cheapest product, the patient most often receives a generic BAK-preserved eye drop. Because the prices change frequently, patients may receive a different product with varying additives at every dispensation. Patients and clinicians alike are not necessarily aware of the potentially varying additives.

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Consequences of substitutions

The generic-substitution law is a particular problem concerning eye drops. BAK is widely accepted as an ocular-surface irritant, causing more side effects than alternative preservatives, such as Polyquad. In a preclinical study on human conjunctival goblet cells, Polyquad did not induce cell death even after 2 hours of exposure, whereas BAK caused significant cell death.[2] With damaged goblet cells or decreased goblet cell density, the risk of ocular discomfort and other adverse effects increases. Thus, when substituting safer preservatives with BAK, the tolerability of the eye drop may decrease. When the tolerability decreases, the risk of poor adherence increases, along with the risk of poor quality of life and decreased disease control. This can be catastrophic for glaucoma patients because it may lead to irreversible visual field defects or even blindness. Other additives, such as phosphates, can also increase the risk of local adverse effects. Furthermore, varying additives may impact the efficacy of the active pharmaceutical ingredient because they may alter the drug uptake.

Law change

Research assessing the damaging effect of BAK has recently led to a change in the generic-substitution law. As of March 2023, the Danish Medicines Agency changed the legislation to state that a generic eye drop cannot contain a different preservative than the branded product. This is a major win for patients and clinicians alike because the safety profiles of branded and generic eye drops now must be more comparable. Patients will likely experience less variation in the tolerability of these eye drops and have increased adherence and confidence regarding their medication. Furthermore, the change underlines the importance of basic research.

References

1. European Medicines Agency, 2007. Generic and hybrid medicines. 2019, from https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/generic-hybrid-medicines, accessed on 10th May, 2023.
2. Hedengran, A., Freiberg, J. C., Hansen, P. M., Jacobsen, J., Larsen, S. W., Harloff-Helleberg, S., Freude, K., Boix-Lemonche, G., Petrovski, G., Heegaard, S., Kolko, M., 2022. Generic benzalkonium chloride-preserved travoprost eye drops are not identical to the branded polyquarternium-1-preserved travoprost eye drop: Effect on cultured human conjunctival goblet cells and their physicochemical properties. *Acta Ophthalmol* 100(7): 819-827.10.1111/aos.15163