Quality of medicines

Quality of misoprostol products

This article presents findings from testing of misoprostol samples, specifically with regard to the percentage of labelled content of active ingredient over time in products packed in different types of blister packs, and makes recommendations for national regulatory authorities and for procurement organizations.

Background

Misoprostol was registered by GD Searle and Co (now part of Pfizer) under the brand name of Cytotec® for the prevention of gastric ulcers associated with non-steroidal anti-inflammatory drugs. There are now many generic misoprostol products available cheaply in low- and middle-income countries, and many (but not Cytotec®) are registered for obstetric indications. Misoprostol is on WHO's Model List of Essential Medicines for use in the induction of labour, incomplete abortion, early abortion (with mifepristone), and for the prevention and treatment of post-partum haemorrhage (PPH) *(1)*.

Misoprostol is a viscous oil, extremely susceptible to degradation. This is ameliorated by using a 1% dispersion of misoprostol in hydroxypropyl methyl cellulose (HPMC), which is considerably more stable and allows the manufacture of tablets with a shelf life of several years at room temperature *(2)*. Nevertheless, exposure to water has been shown to be the principal driver in the degradation of misoprostol in tablets *(3)*, and can occur during manufacture through the use of inappropriate excipients or inadequately controlled environmental conditions. Tablets can also be exposed to moisture depending on their packaging. Polyvinyl chloride (PVC) or polyvinylidene chloride (PVDC)/aluminium blister packs do not provide adequate protection against penetration by moisture, a double aluminium blister pack is therefore recommended *(4)*.

In the past decade there has been a dramatic increase in availability and use of generic misoprostol products worldwide. In addition to its use in early abortion, the international community has been promoting its use in PPH. Unfortunately, this increased availability has not been accompanied by adequate control of the quality of generic products. This was first investigated in 2011 by Concept Foundation, Bangkok, Thailand, and its laboratory subsidiary, Health Concepts International (HCI), with the support of

This briefing note was contributed by:
Peter E. Hall, Managing Director, Health Concepts International / Senior Technical Adviser, Concept Foundation
Navaporn Tagontong, Laboratory Manager, Health Concepts International
Address: Health Concepts International,113 Thailand Science Park, Paholyothin Road, Klong 1, Klong Luang, Pathumthani 12120, Thailand.

Gynuity Health Projects. More recently, studies have been conducted in Nepal and Nigeria and analyses have been performed for several international procurement agencies. This briefing note summarizes the results of both the early study and subsequent analyses undertaken by HCI.

Study design and methodology

In 2011, HCI analyzed 74 samples of misoprostol finished pharmaceutical products collected by Concept Foundation in Bangladesh, Egypt, Cambodia, Kenya, India, Mexico, Nigeria, Pakistan, Peru and Viet Nam. These samples were collected by random sampling from hospital clinics, pharmacies and drug sellers. In 2014-2015, an additional 141 samples collected in Nigeria, Nepal, Pakistan, Bangladesh, Argentina, Indonesia, Peru, the Philippines and Kazakhstan were analyzed. The 121 samples from Nepal and Nigeria were collected by convenience sampling under protocols following WHO guidelines *(4)* from public, social marketing and private sector service outlets, including warehouses, pharmacies, drug sellers, and hospital or clinic dispensaries. The remaining 20 samples were analyzed for the International Planned Parenthood Federation and Marie Stopes International and had been collected by random sampling from clinics or directly from manufacturers.

The tablets were stored below 30ºC until analyzed, at which time the appearance of tablets and their packaging and manufacture dates were documented for all samples, their identity determined, and misoprostol assayed to assess percent of labelled content (LC).

In the absence of a pharmacopoeial method[1], Health Concepts International has developed an analytical method for misoprostol and its principal degradation product, A-type misoprostol, in line with its scope of work accredited under ISO/IEC 17025. The high performance liquid chromatography (HPLC) method was validated and shown to be in conformity with the standard operating procedures instituted under ISO17025:2005 *(6)*. An Agilent HPLC system equipped with a multi-wavelength UV detector was used at a wavelength of 200 nm, with a Poroshell 120 EC-C8 column (4.6 x 75 mm, 2.7µm) and a mobile phase of methanol, water and acetonitrile ratio 40:35:25 v/v/v.

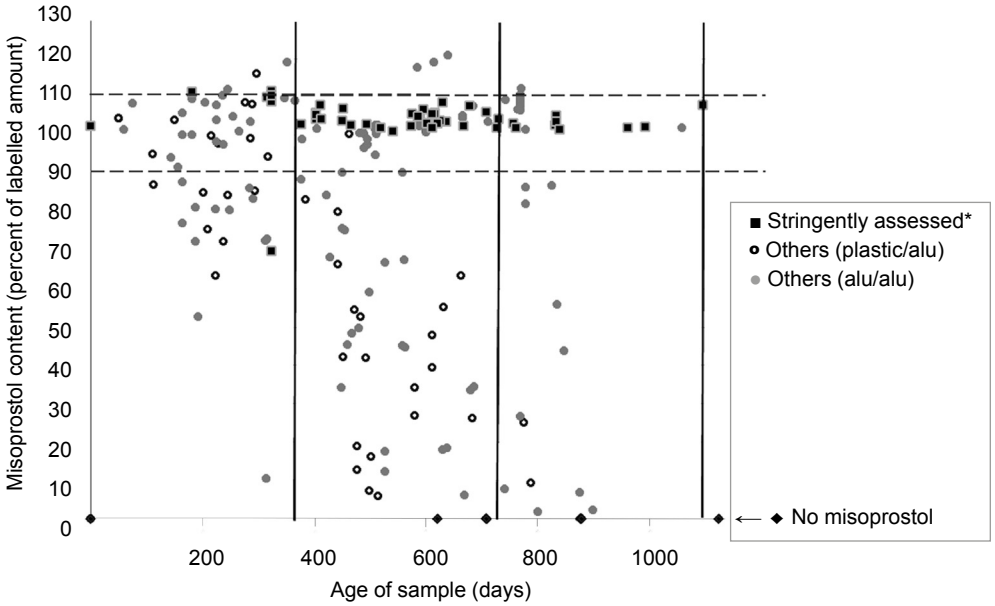
Findings

Of 215 samples analyzed, 119 (55%) were within specifications, containing 90-110% of the labelled content (LC) of 200µg misoprostol, 85 (40%) were below 90% of LC of which 14 contained no misoprostol at all, and 11 (5%) were between 110 and 121% of LC (due to manufacturers' concern of degradation over time). The results are shown in *Figure 1*.

There were 14 samples of product which contained no misoprostol or any of its principal degradation products. Ten samples from one generic company contained no misoprostol and it is not known whether this was a falsified product or whether the issue was due to a quality assurance problem. One sample was from an unidentified manufacturer, and three samples were labelled as the innovator product, Cytotec® (collected in Cambodia,

[1] Note: A draft monograph on misoprostol tablets for inclusion in *The International Pharmacopoeia* has been posted for public comment (Working document QAS/15.643) and is included in the Consultation documents section of this issue of WHO Drug Information.

Figure 1. Misoprostol samples by percent of labelled content (LC) and age



* Approved by a stringent regulatory authority (SRA), WHO-prequalified or assessed by the Expert Review Panel (ERP) and found to be suitable for time-limited procurement to cover unmet needs.

Nigeria and the Philippines); the latter were determined to be falsified products.

Packaging

Fifty samples were packaged in plastic/aluminium (plastic/alu) blister packs, one in a plastic bottle and 164 in aluminium/aluminium (alu/alu) blister packs.

Among the 50 samples packaged in plastic/alu 39 (78%) were out-of-specifications, including 38 samples below 90% LC, 27 below 60% LC and 18 below 30% LC.

Among the 164 samples packaged in alu/alu 58 (35%) were were out-of-specifications, of these 47 were below 90% LC, 27 were below 60% LC and 14 were below 30% LC.

Interestingly, the sample packed in a plastic bottle was within specifications.

Degradation over time

After one year none of the 30 samples packaged in plastic/alu were within specifications, while degradation had occurred in 32 (28%) of 116 samples packaged in alu/alu; the other 84 (72%) were still above 90% LC.

Discussion

The results demonstrate the necessity of packaging in alu/alu blister packs. Nevertheless, packaging in alu/alu in itself is not a guarantee of lack of degradation – 28% of the alu/alu samples showed degradation. Work undertaken by Concept Foundation with manufacturers has shown that if the manufacturing process is not undertaken appropriately and the environment adequately controlled,

humidity may enter the alu/alu blister, causing degradation to occur.

The results did confirm that quality-assured misoprostol products can be manufactured. A total of 51 samples were labelled as products that had passed a stringent assessment, including 41 misoprostol samples manufactured by the innovator and approved by an SRA (three of these samples were determined to represent falsified products), five samples of an SRA-approved mifepristone & misoprostol combination pack, three samples of WHO-prequalified misoprostol and two samples of misoprostol with an Expert Review Panel rating allowing time-limited purchase. Excluding the three samples of falsified product labelled as the innovator product, a total of 48 samples represented stringently assessed products. Of these, one was below 90% LC and two were slightly above 110% LC.

In summary:

- Four out of every ten samples contained less than 90% of the labelled content of misoprostol.
- None of the 50 samples packed in a plastic/alu blister was within specifications after one year.
- Misoprostol packaged in an alu/alu blister pack is not a guarantee of a stable product – 28% of the alu/alu samples showed degradation.
- There was no evidence that 14 samples had ever contained misoprostol, three of these were falsified products labelled as Cytotec®.
- Only one of 48 samples of products that had passed a stringent assessment had a labelled content of misoprostol below specifications.

Recommendations

For national authorities

It is essential that a survey of products available in the country is undertaken and sub-standard products removed from the market.

For procurers

Product in PVC or PVDC/aluminium blister packs should never be purchased. It has been documented that they allow moisture to enter the blister pack, and no product analyzed met specifications after one year.

It is essential to obtain evidence of the quality, and in particular, the stability of product from the manufacturer before ordering. Preshipment testing is pointless for inappropriately manufactured and packaged product – the product may comply with specifications shortly after manufacturing but may only have 50% of labelled content within six months.

As quality-assured products (prequalified by WHO or approved by an SRA) become available, national and international procurers should ensure that they purchase these products.

References

1 WHO. The Selection and Use of Essential Medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). WHO Technical Report Series No 994. Geneva, World Health Organization; 2015.

2 Collins PW. Misoprostol: Discovery, development and clinical applications. Medicinal Res Rev. 1990,10:149-172.

3 Berard V, Fiala C, Cameron S, Bombas T, Parachini M, Gemzell-Danielsson, K. Instability of Misoprostol Tablets Stored Outside the Blister: A Potential Serious Concern for Clinical Outcome in Medical Abortion. PLoS ONE 2014; 9(12): e112401. doi:10.1371/journal.pone.0112401.

4 Carman-Meakin B. Re: Blister Packing – PVC/PVDC foil [contribution to GMP Forum online platform, 19 January 2007, available at www.pharmweb.net/forum/0100/2007/msg00027.html] and personal communication by telephone with Dr Carman-Meakin.

5 WHO. Guidelines on the Conduct of Surveys of the Quality of Medicines. Working document No. QAS/15.630. Adopted by the Expert Committee on Specifications for Pharmaceutical Preparations at its 50th Meeting with amendments as agreed during the meeting.

6 ISO/EC 17025:2005. General requirements for the competence of testing and calibration laboratories. International Standards Organization, Geneva; 2005.