Antimalarial drug resistance and the importance of drug quality monitoring

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ABSTRACT

The availability of counterfeit and poor quality drugs contribute to resistance and erroneous efficacy study results as well as directly affecting the health of individuals. This report describes the importance of drug quality monitoring as part of a comprehensive disease surveillance program.

Problem of Resistance

Observed treatment failure may result from either actual drug resistance or sub-therapeutic levels. If treatment failure is not a direct result of resistance, then exposure of organisms to suboptimal levels of drug will certainly contribute to developing resistance. Systemic drug levels are influenced by metabolism, absorbance, compliance or drug quality. For example, age, genetics, drug interactions, diet and disease state affect metabolism and absorption rates, while high drug costs, inconvenient dosing regimen and side-effects have an adverse influence on compliance. Also, administration of poor-quality or counterfeit drugs can expose a patient to insufficient levels of active ingredients. Although pharmacokinetic parameters such as absorption and metabolism are difficult to control, diligent monitoring of drug quality can ensure that the correct dose of active ingredient is being administered.

Even if antimalarial drugs are of good quality, overuse or under-dosing influences drug resistance. Cheap and commonly available antimicrobials are more likely to be prescribed, thereby increasing the chances of resistance.

Since these medications are prescribed more often, the probability of inappropriate dosing regimens is increased. Also, due to high availability, these drugs are more likely prescribed only to placate the patient, regardless of an accurate diagnosis. Under-dosing typically results from an incomplete drug course either due to the expense of the drug or because the patient feels better and assumes the drug is no longer needed. Also, an incorrect dosing regimen may result from a misdiagnosis or other misguided judgments made by a healthcare professional. Another grave concern influencing resistance is the availability of substandard and counterfeit pharmaceuticals. Substandard quality most often occurs in inexpensive medicines where quality control is not a big priority and profits are made by selling in volume. Expensive medicines such as “lifestyle drugs”...
as well as many newer antiviral and antimicrobial drugs are prone to be counterfeited.[7]

Problem of Counterfeit Drugs

According to the world health organization (WHO), a counterfeit drug is a “medicine which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient ingredients or with fake packaging”.[3] Substandard drugs are genuine products which have not passed the quality testing protocols previously set for each product. The testing protocols and specifications are published in official pharmacopoeias such as the United States Pharmacopeia (USP), the European Pharmacopoeia and the WHO International Pharmacopoeia. Also, many countries have published their own pharmacopoeias. The WHO has reported that up to 25% of medicines consumed in developing countries are counterfeit or substandard.[9] Although, there are many reported cases of counterfeit pharmaceuticals, particularly lifestyle drugs and antimicrobials, antimalarials have become a particular favorite of the counterfeiters who prey upon the poor and ill-informed populace of the developing countries.[2-5,10]

Not only do counterfeit and substandard drugs undermine the health profession and damage pharmaceutical companies, they hamper accurate interpretations of drug efficacy studies. In an investigation of the quality of essential drugs in the Tanzanian market, two out of the four tested sulfadoxine/pyrimethamine (SP) tablets failed the USP requirements for pyrimethamine dissolution.[11] In dissolution testing performed in our laboratory, we have also observed dissolution failure of pyrimethamine in SP samples obtained from Africa. Along with a consistent dose of active ingredients, dissolution is another parameter important in drug quality. Drug dissolution is a process in which the active ingredient of a drug formulation enters into a specified solvent and the dissolution rate is an indicator of in vivo drug performance (bioavailability). Although the amount of active ingredients per dosage form may pass USP standards, dissolution of active ingredients many a times fails due to improper formulation or changes in the physico-chemical characteristics of the formulation resulting from degradation or poor storage conditions.

Drug Quality Monitoring

The problems of quality failure often occur in resource-poor countries lacking effective drug regulatory agencies and proper drug quality testing laboratories. A drug quality assurance system relies on the ability to identify counterfeit or poor quality pharmaceuticals. [7] Typically, a product is tested to confirm the identity and potency using the specifications and methods described in pharmacopoeias. Unfortunately, the more sophisticated analytical methods described in the pharmacopoeias are not feasible in many countries due to a lack of required instrumentation and proper reagents. A rapid and inexpensive technique to initially screen for a suspicious product is to use one’s own senses. Poor-quality printing and inconsistent coloration of the package or inserts provide obvious clues. Also, one should be suspicious of pharmaceutical dosage forms having a peculiar odor, taste or consistency.[12] Genuine products should be available for direct comparisons. The sophistication of counterfeiters has developed to a degree where packaging and dosage forms are practically indistinguishable from the original. Very often the only distinguishing feature of counterfeits is that they contain little or no active ingredient. In many circumstances, a small amount of active ingredient is sometimes added to produce a positive qualitative test. Thin-layer chromatography (TLC) and colorimetric methods provided quantitative and qualitative tests to help identify counterfeit as well as substandard pharmaceuticals. Compendiums of TLC and colorimetric techniques are available for most essential drugs.[11-17]

Recommendations and Conclusions

In a recent review article of counterfeit drugs, it is recommended that inexpensive or free good-quality medicines should be readily available in countries having poor or absent drug regulation. Urgent support is needed in these countries so that monitoring of drug quality can be an intrinsic part of their disease surveillance programs. It should be a legal requirement to report any substandard or counterfeit drug to the respective national drug regulatory authority and severe penalties should be enforced for those knowingly engaged in the manufacturing of counterfeit medicines.[7] The Indian government has recently considered imposing a death penalty for counterfeit drug manufacture.[18] This action is a big step relative to the current penalty of no less than three years imprisonment and a fine of US$108.[19]

The rampant availability of counterfeit and poor-quality pharmaceuticals significantly impacts the healthcare of developing countries, not only because of the direct consequences of treatment failure, but the contributions substandard drugs make towards developing resistance. Until analytical capacity is improved, low-cost methods such as TLC and colormetry are useful in providing drug regulatory agencies with rapid information on drug quality.

References

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