Chapter 2: An overview of Quinine Sulfate

Introduction

Quinine is an ancient API found in the bark of the Cinchona tree (refer to Figure 2-1). This evergreen tree originates from the forests of the eastern slopes of the Andes Mountain (Kaufman & Rúveda, 2005:856). According to legend, a native Indian, suffering from a fever, drank from a pool of stagnant water. Realising that the water had been contaminated with surrounding quina-quina trees he first thought he was poisoned. Surprisingly, his fever soon subsided and he shared his accidental discovery with fellow villagers. Since then, the native indians of Peru have used the quina-quina tree for its anti-pyretic properties (Achan *et al.,* 2011:144). Word spread fast and the first shipments of cinchona bark arrived in Spain in 1636 (Sullivan, 2012:46) introducing quinine to Europe for the treatment of malarial fever. In 1677 the bark was officially introduced in the London Pharmacopoeia and since 1681 universally accepted as an anti-malarial substance (Kaufman & Rúveda, 2005:856).

Figure 2-1: Photographs of the Cinchona tree (left), Cinchona bark (middle) and powdered Cinchona bark (right) (Sarah, 2010).

It was not until 1820, that quinine was extracted and isolated from the bark of the cinchona tree. Before this the bark was dried, ground to a fine powder and mixed with wine (Achan *et al.,* 2011:144). The four active alkaloids that can be extracted from the bark are: quinine, quinidine, cinchonine, and cinchonidine. All of the aforementioned alkaloids are effective in treating malaria (Achan *et al.,* 2011:144; Sullivan, 2012:46).

2.1 Chemical, pharmaceutical and pharmacological properties of quinine

2.1.1 Classification of quinine

Alkaloids are naturally occurring amines derived from plant sources with slightly basic properties (McMurry, 2003:397). Quinine forms part of the cinchona alkaloid family and because of its basic properties it commonly presents as a salt such as a sulfate or a dihydrochloride (Achan *et al.,* 2011:145).

Quinine is a quinoline-alcohol and contains in its structure a quinoline nucleus and an amino alcohol side chain (Rosenthal & Goldsmith, 2001:887; Rang *et al.,* 2003:678). Of specific interest to this study is quinine sulfate or chemically, (8",9R)-6'-methoxycinchonan-9-ol sulfate dehydrate (Figure 2-2).

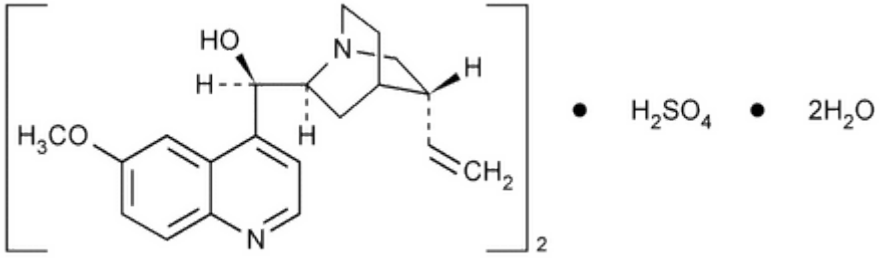

Figure 2-2: Structure of Quinine sulfate (USP, 2012).

2.1.2 Extraction of quinine

There are about 90 varietals of the Cinchona tree, which differ in the content of extractable/available quinine (between 5 - 10%). The first extraction (by Pierre Joseph Pelletier and Joseph Caventou) was a process of crystal purification: pulverized bark was soaked in acidified water, resulting in the crystallisation of quinine. Later on, another extraction process was developed in India where 100 parts of powdered bark was mixed with 8 parts of caustic soda, 500 parts water and 600 parts fuel and kerosene oil (Sullivan, 2012:46).

The alkaloids would diffuse into the oil and the oil would be transferred to heated acidified water, and then cooled for crystallisation. Sulfuric acid was used to produce quinine sulfate and hydrochloric acid for quinine hydrochloride (Sullivan, 2012:46).

2.1.3 Synthesis of quinine

The quest to synthesise quinine started in the 1800's but the complexity of the structure made it difficult. Today the synthesis of quinine is possible, but not cost effective, and duly the extraction from the cinchona bark remains the primary source for quinine (Dollery, 1999:Q16; Sullivan, 2012:48).

2.1.4 Chemical properties of quinine sulfate

The molecular formula of quinine sulfate is $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ and it has a molecular weight of 783.0 g/mol (Strauch *et al.,* 2012:500). Quinine sulfate is described as white or almost white crystalline powder which darkens on exposure to light and has a melting point of approximately 225°C (Reynolds *et al.,* 1993:408). According to Strauch *et al.* (2012:500-501) quinine sulfate does not seem to exhibit polymorphism. The pH of a 10 mg/ml suspension in water ranges between 5.7 and 6.6 (Reynolds *et al.,* 1993:408). Quinine has pKa values of 4.1 and 8.5 at 20°C and is a weak base (Strauch *et al.,* 2012:502).

2.1.5 Commercially available dosage forms of quinine sulfate

Quinine sulfate is available in solid oral dosage form (tablets and capsules), typically as 200 mg or 300 mg quinine sulfate per tablet/capsule. Quinine is also available as an injection, in the hydrochloride form, in concentrations of 300 mg/ml quinine hydrochloride (Dollery, 1999:Q17). Preparations should be stored at room temperature, protected from light and most manufacturers specify a shelf-life of 3 to 5 years (Dollery, 1999:Q18). Some examples of the quinine sulfate and quinine dihydrochloride dosage forms are shown in Figure 2-3.

Figure 2-3: Examples of FPP containing quinine;(A) Quinine sulfate 300 mg tablets, (B) Quinine dihydrochloride ampoules for injection and (C) Quinine sulfate capsules 324 mg (RxResource.org, 2013 ; Wu Han Grand Pharmaceutical Group Co. Ltd., 2013 ; Reliable Canadia).

2.1.6 Solubility

Literature describing the solubility of quinine sulfate is limited. Quinine is generally described as slightly soluble in water and sparingly soluble in boiling water. According to Strauch *et al.* (2012:501) the solubility data of quinine sulfate in the pH range 1.0 – 7.5 at 37°C is incomplete, and most sources only report the solubility in water, alcohol or chloroform (Reynolds *et al.,* 1993:408).

The Biopharmaceutics Classification System (BCS), classify API's into one of four classes, taking the compounds aqueous solubility and permeability into consideration (Shargel *et al*., 2005:482). Lindenberg *et al.* (2004:267) classified quinine sulfate as a BCS class I or III API whereas Strauch *et al.* (2012:504) assigned quinine sulfate as a BCS class I or II API (Strauch *et al.,* 2012:504). The controversy surrounding the BCS classification is discussed in more detail in Chapter 6.

2.2 Pharmacology

2.2.1 Indications

Quinine is indicated for the treatment of malaria infection incurred by any of the four plasmodium species (Rosenthal & Goldsmith, 2001:883*).* Unlike other anti-malarial treatments of the same generation (older medicines), quinine still plays a vital role in the treatment of malaria in Sub-Saharan Africa and other malaria endemic countries and seems to be the anti-malarial of choice:

- in the treatment of severe malaria (Achan *et al.,* 2011:145);
- where chloroquine-resistance is suspected (Dollery, 1999:Q16);
- for the treatment of cerebral malaria (Dollery, 1999:Q16) and
- in the first trimester of pregnancy together with clindamycin (Achan *et al.,* 2011:145).

2.2.2 Pharmacokinetic properties

Quinine is rapidly and almost completely absorbed from the gastrointestinal tract with absorption rates from quinine sulfate tablets of up to 90% (Strauch *et al.,* 2012:502; Sullivan, 2012:59). The peak plasma level of quinine is reached within 1 - 3 hours after oral administration and is widely distributed in body tissues. In patients suffering from severe malaria the half-life of quinine is longer (18 hours) comparing to healthy controls (11 hours), due to the reduction in hepatic clearance (Rosenthal & Goldsmith, 2001:887; Sullivan*,* 2012:59). Quinine is metabolised in the liver and the metabolites are excreted in the urine (Rang *et al.,* 2003:678).

2.2.3 Mechanism of action

As mentioned in Chapter 1 (section 1.1.5), quinine is a blood schizonticidal agent, which makes it effective against erythrocytic forms of the malaria parasite (Rang *et al.,* 2003:678; Rosenthal & Goldsmith, 2001:887*)*. The malaria parasite uses hemoglobin within the erythrocytes of the host as sustenance. Quinine accumulates in the acid food vacuole of the malaria parasite where it inhibits the hemepolymerase enzyme. The hemepolymerase enzyme is necessary to convert toxic heme (from hemoglobin) into hemozoin. As a result the heme accumulates within the parasite and the parasite's life cycle is brought to an end (Dollery, 1999:Q16).

2.2.4 Indicated treatment dosage

When uncomplicated malaria is treated, it is recommended that 10 mg/kg of quinine sulfate be taken three times a day for 7 - 14 days.

When quinine treatment is combined with clindamycin or doxycycline, the dosing regimen may be shortened (Sullivan, 2012:59). If a patient suffers from severe malaria infection, quinine dihydrochloride is administered intravenously. In adult patients, a loading dose consisting of 20 mg/kg of quinine dihydrochloride is administered followed by infusion 10 mg/kg every 8 hours. The infusions should be administered over a period of 2 - 4 hours. Quinine dihydrochloride may also be administered via intramuscular injections if diluted 1:1 with sterile saline (Sullivan, 2012:60).

2.2.5 Side effects

Quinine has a bitter taste and may irritate the gastric mucosa causing nausea and vomiting. Most patients also experience some form of cinchonism (Rosenthal & Goldsmith, 2001:887). Cinchonism is associated with symptoms such as dizziness, tinnitus, headache and blurring vision. High plasma levels of quinine may result in hypoglycemia, hypotension, cardiac dysrhythmias and coma (Rang *et al.,* 2003:678). A hypersensitivity reaction to quinine ("Blackwater fever") may occur and result in hemolysis and hemoglobinuria (Rosenthal & Goldsmith, 2001:888*)*.

2.2.6 Interactions

The absorption of quinine may be inhibited when taken in conjunction with aluminium-containing antacids. Quinine inhibits the liver enzyme, cytochrome P_{450}2D6, thus it should be taken into consideration when a patient is on any medication that may be metabolised via this pathway e.g. warfarin (Sullivan, 2012:60).

2.2.7 Contra-indications

Patients who have a history of cardiac abnormalities or underlying visual or auditory problems should preferably not use quinine. Furthermore, it is necessary to adjust the dosage should the patient suffer from renal insufficiency (Rosenthal & Goldsmith, 2001:888). Diabetic patients should preferably not use quinine as it may induce insulin production (Dollery, 1999:Q19).

2.2.8 Safety and toxicity

Quinine is described as relatively safe if the correct dosages are taken or if infused slowly (Dollery, 1999:Q19).

2.2.9 Failure of quinine treatment

The most common causes of quinine treatment failure are inadequate compliance with a full course of therapy or the use of poor quality medicine. Counterfeit or substandard medicine or variations in dose have been detected with the cinchona alkaloids for centuries (Sullivan, 2012:50).

2.2.10 Resistance to quinine

The spread of quinine resistance has been sporadic and not sustained. Quinine is a substitute treatment in areas where chloroquin resistance is evident (Sullivan, 2012:51).

Conclusion

The purpose of this chapter was to provide a brief overview of the history, chemical-, pharmaceutical- and pharmacological properties of quinine sulfate.

Despite quinine being one of the oldest anti-malarial treatments, it is still widely used for the treatment of malaria to this day. Quinine (sulfate) is described as an “old” medicine allowing for an increasing probability that its physico-chemical profile may be lacking in accuracy. It is evident from current literature that controversy surrounds the solubility of quinine sulfate.

With sufficient background on malaria, quinine sulfate and the importance of QC, the study continues to Chapter 3, which describes the materials, methods and equipment used during this study.