WHETHER FMD AFFECTS CYTOCHROME P₄₅₀ SYSTEM IN LIVER OF COW! – A CASE REPORT

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Metabolism of ceftriaxone with milk excretion of its active metabolite (ceftizoxime) was evaluated in a crossbred cow which was suffering from mastitis just after recovery from foot and mouth disease (FMD) following a single intravenous dosing of 1.5 gm of ceftriaxone. It was reported earlier that the major active metabolite i.e. ceftizoxime is mainly excreted through milk, not the parent (ceftriaxone) in cows. The FMD affected lactating cow was diagnosed by a registered veterinarian on the basis of clinical signs such as high temperature, excessive salivation, formation of vesicles on the oral and nasal mucosa, the inter-digital spaces and coronary bands on the feet. However, just after recovery, the crossbred cow was observed to suffer from acute mastitis with milk containing flakes and other clinical signs. The milk showed deep green colour on Bromo Thymol Blue paper test. The cow was administered a single dose of ceftriaxone (1.5 gm) intravenously and milk was collected at different times interval. The milk samples were analysed for estimation of ceftriaxone/ceftizoxime by UV-Vis Spectrophotometer. Only ceftriaxone was detected in milk starting from 20 minutes to 72 hr post dosing, but ceftizoxime could not be detected. The observation may be correlated with liver impairment in FMD affected cows and possible inhibition of cytochrome P₄₅₀ in liver as ceftriaxone is metabolised through induction of cytochrome P₄₅₀ to its active metabolite i.e. ceftizoxime.

Key words: Ceftriaxone, Crossbred cow, Cytochrome P₄₅₀, FMD, Mastitis

In cows, infection of udder and teats may progress to mastitis that causes milk loss (Govindaraj *et al.*, 2017). A total of 1,082 FMD outbreaks were reported in the state

of West Bengal, India during the 18 years from 1985 to 2002 (Bhattacharya *et al.*, 2005). The liver impairment and alterations in AST, ALT and alkaline phosphatase in

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FMD in cattle has been studied earlier in cattle (Gattani *et al.*, 2011). The alterations at different times in alkaline phosphatase, AST and ALT have also been reported (Sar *et al.*, 2018b). However, cytochrome P₄₅₀ (a delicate drug metabolising microsomal mixed function oxidase system) inhibition has not been reported yet.

The cross bred cow was brought by a farmer from Haringhata, Nadia. The cow was of 4 years age producing average 4 kg of milk per day. The lactating crossbred cow was diagnosed to suffer from mastitis on the basis of clinical signs including painful swelling of the udder, hotness and hardness of the udder, milk containing flakes. One drop of milk was given on BTB (Bromo Thymol Blue) paper spot subsequently. The BTB paper spot showed deep green colour confirming mastitis. The cow was reported to recover from FMD few days back before incidence of mastitis which was diagnosed by reported characteristic clinical signs.

Upon diagnosis of mastitis, the cow was administered a single dose of ceftriaxone (a broad spectrum third generation cephalosporin) at a total dose of 1.5 gm of powder dissolving in 10 mL of distilled water through jugular vein. 1.5 mL of milk samples were collected by hand

milking following liquid soap washing at '0' (pre drug), 5 min, 10 min, 15 min, 20 min, 30 min, 40 min, 1 hr, 2 hr, 24 hr, 48 hr and 72 hr. Milk samples were analysed as per reported UV-Vis spectrophotometric method (Sar *et al.*, 2006). The processed milk samples were analysed by SPECTRASCAN UV 2600, Chemito, Mumbai, India.

Milk samples collected before drug administration were cultured for identifying the causative organisms (Quinn *et al.*, 1994). Culture test exhibited significant number of *Staphylococcus albus* (coagulase negative) and few colonies of *Staphylococcus aureus* after 48 hrs of incubation at 37°C. However, culture in MacConkey's Agar did not show any growth after 48 hr of incubation at 37°C.

The concentrations detected at 20 min, 2 hr, 48 hr and 72 hr were 2.0 µg/mL, 1.8 µg/mL, 3.5 µg/mL and 53 µg/mL of ceftriaxone, respectively (Fig. 1). No ceftizoxime (active metabolite of ceftriaxone) could be detected at any other time of collection. The concentration of ceftriaxone at different time indicated inhibition of metabolism of ceftriaxone by cytochrome P₄₅₀ in liver. But, only ceftizoxime (metabolite of ceftriaxone) was detected in lactating cows following single

Fig. 1. Semilogarithmic plot of concentrations of ceftriaxone in the mastitic cross bred cow following single intravenous injection of 1.5 gm of ceftriaxone

intravenous dosing of ceftriaxone to mastitic cows (Sar *et al.*, 2010).

Ceftriaxone having a molecular weight 554.59 is liable to undergo enterohepatic circulation and may undergo metabolism through cytochrome P₄₅₀ in liver (Sar *et al.*, 2018a). The metabolism of ceftriaxone was inhibited in carbon tetrachloride induced hepatopathic goats as ceftriaxone is mainly metabolised in the liver. Only ceftriaxone was detected in urine of goats following a single intravenous dosing of ceftriaxone in hepatopathic goats (Sar *et al.*, 2013). It was also reported earlier that only ceftizoxime, not ceftriaxone was excreted through milk in goats and cows in our previous studies (Sar *et al.*, 2006, 2010, 2018a). Ceftriaxone metabolism was not inhibited during

mastitis in any of our previous study (Sar *et al.*, 2006, 2010, 2018a) which clearly indicates interference in cytochrome P₄₅₀ enzyme system due to prior FMD infection in this cow. Sar *et al.*, 2018b also reported alterations in serum AST, ALT and alkaline phosphatase activity during different days of FMD infection in lactating cows.

Availability of only parent ceftriaxone in milk in this particular crossbred cow which was suffering from acute mastitis strongly indicated interference/inhibition of cytochrome P₄₅₀ in liver of cow as a result of its prior FMD infection. However, due to lack of infrastructure, urine of the cow could not be collected for drug assay. These findings clearly correlate inhibition of cytochrome P₄₅₀ component in liver which warrants further research.

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