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Review

Chloramphenicol Toxicity: A Review

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Abstract

Chloramphenicol (CAP) is a potent and efficient antibiotic used since years against many pathogens. Despite being highly effective, it shows severe toxicity in the form of Aplastic anemia (AA) and bone marrow suppression. Its D – form is the toxic one and inhibits protein synthesis. In living system, CAP is hydrolyzed and absorbed completely. Its excretion is also at a high rate but is highly impaired in disorders associate liver and kidneys. It is metabolized in liver to Chloramphenicol glucuronide. Being highly toxic, it is still prescribed at a noticeable rate. It is recommended to be prescribed to be only when there is no other alternative is present with a monitoring of its concentration in patients body. Chloramphenicol induced hematotoxicity was demonstrated in rats which recovered due to oral administration of coconut water within two weeks.

Keywords: Chloramphenicol, Toxicity, Antibiotic, Aplastic Anaemia, Hematotoxicity.

INTRODUCTION

Chloramphenicol (CAP) is a broad spectrum antibiotic, was first quarantined from bacterium*Streptomyce svenezualae* in the year 1947. It was available by the trade name of Chloromycetin by Parke Davis & Co. It was prescribed in mass in 1948 in USA following g an outburst of enteric fever. In 1949 it was available by the trade name of Chloromycetin by Parke Davis & Co. It was prescribed in mass in 1948 in USA following an outburst of enteric fever. In 1949 it was cleared from Federal Food and Drug, since then it has been used and worked upon extensively. Being a potent inhibitor of protein synthesis (Cundliffe, E.,McQuillen, K., 1967). It is extremely useful and active against a variety of pathogens including bacteria, *Spirochaetes*, *Rickettsiae* (Harrel, G. T., 1952;Smadel, J. E., Jackson, E. B., 1947 (a);Smadel, J. E., et al., 1949 (b);McClean,J.W.,*et al*., 1949),*Chlamydiae* (Harrel, G.T., 1952), Mycoplasmas (Denny, F.W., *et al.* 1971*), Tryponemapallidum* (Smadel, J. E. *et al.* 1949 (b); Romansky, M. J.,*etal.,*1949), *Borrelia*(McClean, J. W.,*et al.,* 1949), Leptospira (Romansky, M. J.,*et al.,*1949), *Pseudomonas pseudomallei* (Howe, C., *et al.,* 1971) and *Actinomyces* (McClean, I. W. ,*et al.,* 1949). It has bacterial action against *Haemophilus influenza* (Wehrle, P. F., *et al*., 1967; Overturf, G. P. *et al*., 1975; Rahal, J. J., Jr., Simberkoff, M. S., 1979),*Streptococus pneumonia* (Wehrle, P. F., *et al.,* 1967; Rahal, J. J., 1979) and *Neisseria meningitidis* (Wehrle, P. F., *et al*., 1967; Rahal, J. J., 1979). It shows no activity against parasites, fungi, mycobacteria and *Pseudomonas aeruginusa*.

Chemistry

Chemically chloramphenicol is D-(-)-threo-1-p-nitrophenyl-2-dichloroacetamido 1,3-propandiol. It is in the form of a white, crystalline, neutral compound that is completely soluble in alcohol and is water insoluble. Chemically, it has two chiral centers leading to its four stereoisomers which include D – erythro and L – erythro isomers. Out of these, D – erythro has 98% bacteriostatic potency, whereas, L – erytro has only 2%. This is because of the fact that proteins have L – amino acids and D – erythro isomers fits in it due to its geometry and thus acts as protein synthesis inhibitor. CAP is available in two esterified forms; Palmitate and Succinate, both are ineffective against microbes (Glazko, A. J., *et al.,* 1952 (b); Ross, S., *et al*. 1952). CAP is tasteless in suspension whereas, CAP Succinate is water soluble

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ester suitable for *iv*use.

Pharmacology:

Route of administration has no effect on CAP metabolism in the biological system. Esters of CAP has different hydrolysis patterns which is very rapid (Glazko, A. J., *et al*., 1952 (b); Ross, S., *et al.* 1952). In a study, 8 cats were provided the ocular application of 1% CAP ointment at 8 hour interval for 21 days, at the dose levels of 2.7 mg/cat/day. On 21st day plasma concentrations were measured to be .09 µg/ml (Conner, G. H., Gupta, B.N., 1973). CAP succinate is hydrolysed by liver, lungs and kidneys (Pickering, L. K., *et al.,* 1980). CAP palmitate is hydrolysed to CAP prior to gastrointestinal absorption. Crystalline CAP is resorbed rapidly and almost completely from gastrointestinal tract (Glazko, A. J., *et al.,* 1952 (b)). CAP is metabolized primarily in liver to CAP glucuronide which has no known toxicity (Glazko, A. J., *et al.,* 1949 (a)).

Absorption of CAP is complete (Sutherland, J. M., 1959; Glazko, A. J., *et al.,* 1968 (c)) with a total body clearance of 0.122 – 0.429 liters/kg/hr (Sack, C. H., *et al.,* 1980). HPLC analysis revealed that the biotransformation of CAP takes place by oxidation, reduction and conjugation (Holt, D. E., 1995). CAP Succinate is converted into CAP, nitro – CAP and other metabolites after 1 hour and 15 minutes of administration (Ambekar, C. S., *et al.,* 2000).

Most of the CAP is completely metabolized, remaining 5 – 10% is excreted unchanged in urine by glomerular filtration (Glazko, A. J., *et al.,* 1949 (a); Ley, H. L., *et al*.,1948) and 0.14% in bile (Glazko, A.J., *et al*., 1949 (a)). Similar to other antibiotics, CAP is also eliminated by kidneys (Lindberg, A. A., *et al.,*1966). Maximum concentration and speed of elimination are proportional to dose administered (Glazko, A. J., *et al.,*1952 (b)).

Half-life:

Half Life of CAP varies with age and clinical manifestations. In normal adults, CAP has a half-life of 1.6 – 3.3 hours (Kunin, C. M., *et al*., 1959) whereas in neonates it is 0.87 – 17.8 hours (Friedman, C. A., *et al.,* 1979). In anuric adults half-life increases upto the 3.2 - 4.2 hours (Kunin, C. M., *et al.,* 1959) with an accumulation of CAP glucuronide.

In cases of liver disorders (totally or partially impaired liver functions) CAP metabolism is highly impaired (Azzollini, F., *et al.,* 1972; Koup, J. R., *et al*., 1979 (b)) and half-life may increase up to 3 – 12 hours (Kunin, C. M., *et al*., 1959). In neonates, serum levels reach very high up to 313 µg/ml (Suazer, C. R., *et al*., 1992). Renal impairment has no effect on the elimination rate of active and potentially toxicity free drug (Goodman and Gillman,1992).

CAP in food and food industry:

Some studies suggest the use of CAP in food. Although, most countries have banned CAP from animal food production, still traces of it have been detected in shrimp and other aquaculture products. According to regulations promulgatedin 1980's and 1990's, use of CAP in food was banned and countries have established a zero tolerance policy. In Japan, zero tolerance thresholdfor CAP is 50 ppb which in USA is 5 ppb. Meat and offal from treated animals contained CAP and its non – genotoxic metabolites (Milhaud, G., 1993).

Interaction with other drugs:

In general, CAP inhibits metabolism of other drugs such as tolbutamide ,diphenylhydantoin, dicumarol and penicillin (Christensen, L. K.;Saovstev, L., 1969; Koup , J. R. , *et al.,*1978 (a); Jatwetz, E., *et al*., 1951), phenobarbitol and paracetamol being an exception. Use of CAP and phenobarbital results in unexpectedly high levels of phenobarbitol in serum (Koup, J. R. , *et al.,* 1978 (a)). Paracetamol has no effect on CAP metabolism (Paap, C.H., Nahata, H. C., 1990) with no change in its half-life and plasma concentration (Stein *et al*., 1989).

CAP and Aplastic anaemia :

Even being a potent antibiotic with a broad range of spectrum, the use of CAP is limited due to its association with aplastic anaemia (AA) (Rich, M. L.,*et al*., 1950) and bone marrow suppression (Amberkar, C. E., *et al.,* 2000). AA is a rare, dose independent , irreversible, idiosyncratic, manifestationof CAP which in most cases is seen years after the treatment (Younis, A.A. ,1989 (b)) and is fatal (Turton, A. A., 2002) risk of developing AA after CAP administration is 1:30000 to 1:5000015 (Li,C.H, *et al.,* 2010).

CAP associated AA cannot be predicted by the monitoring of blood cell counts. Percent mortality is around ~50% and in neonates it is ~ 40 % (Suazer C. R., Ow,E. T., 1992). Prognosis is poor, if AA develops after a long time of treatment (Polak, B. C. P.,*et al*, 1972). Studies suggest the higher occurrence of AA in black patients (Best, W. R.,1967; Wallerstrein,R.O*., et al*,1969). Only orally administered CAP leads to AA (Holt, R., 1967; Gleekman, R. A., 1975) This has made the CAP to be prescribed parenterally by many physicians. It is not known whether this lowers the incidence of AA or not but yes the risk is obviously lowered. Other than oral and parenterally absorbed CAP, it is also used as ophthalmic preparations where AA is also very rare (Rosenthal, R. L.,Blackman, A., 1965; Carpenter, G., 1975; Abrams,

S. M. et al., 1980)

Mechanisms Involved in CAP induced AA:

Earlier, AA was hypothesized to occur due to genetic metabolic defect or the manifestation was theorized because of the genetic predisposition of the being. The theory states CAP induce and enhances these defects which results in damage to undifferentiated marrow stem cells (Cronkite, E. P., 1964)

A different theory suggests that certain enteric bacteria can produce a specific enzyme that degrades CAP to a toxic product (Holt, R., 1967). This was suggested by further studies, which suggests that the metabolites of CAP generated by intestinal bacteria undergo further metabolic transformations in system with *in situ* production of toxic intermediate (Yunis, A. A., 1989 (b)) Rarity of these enzyme producing enteric bacteria explain the infrequency of AA.

In a study (Yunis, A. A, 1973 (a)) it was actually revealed that the p-nitrosulfathiazole group is responsible for AA by inhibiting DNA synthesis in marrow stem cells. This theory was based on the observation that thiamphenicol which is a CAP derivative, does not have a p-nitrosulfathiazole group and does not cause AA and thus, extensively used in Europe. This theory was further supported by studies indicating CAP reduced to p-nitrosulfathiazole which is a short lived reduction intermediate and leads to helix destabilization and strand breakage (Irena, M. S. et al., 1983) except than being unstable. These intermediates are highly toxic (Eyer P. et al., 1984)

At a concentration of 2000-4000 µg/ml CAP depressed phagocytosis and burst activity of neutrophils (Paape, M. J. et al., 1990). Other studies suggests that CAP directly induce apoptosis in haematopoietic stem cells, directly leading to AA (Kong C. T., et al., 2000).

In a study, Chloramphenicol was administered at dose levels of 150 mg/kg in rats for 14 days which caused significant haematotoxicity characterized by decrease in RBC count, Hb% and WBC count which were indicators of anemia. (Dubey, Chetan, *et al*., 2011)

Clinical Usage and Prescriptions:

In 1952 (3 years after giving the “safe to use” certification to CAP) FDA conducted a survey on the association of CAP to AA. This resulted in the finding that the 68% of the population with prolonged therapy to CAP has one or the other type of blood dyscariasis (Lewis C. N. et al., 1952). Afterwards, labels were required with the warning that blood dycariasis may be associated with the intermittent or prolonged use of CAP. Practitioners were instructed not to prescribe it intermittently. It is to be used for a very few serious and potentially fatal infections against which no safer alternative is present. As in earlier, this drug had been prescribed for inappropriate or trivial infections such as common cold, bronchitis, tonsillitis and acne, (Best, W. R.,1967). In neonates it was prescribed at doses higher than those recommended for older subjects (Weiss, C. F., *et al.,* 1960)

After the warning signal being presented there is a noticeable decrease in AA cases. CAP is still prescribed especially in the treatment of *H. influenza* which is ampicillin resistant (McGowan, J. E., *et al*., 1976). It is also used to treat infections caused by Vancomycin resistant enterococcoi that are resistant to other antibiotic regimes. It is also a drug of choice in penicillin resistant meningitis caused by *H. influenzae, S.pneumoniae* and *N. meningitides* (Westenfelder, G.O., *et al.,* 1969). CAP is still being used in endemic areas (at dose levels higher than the permittable ones) which is suggested by the decline in resistance to multi drugs by the strains of *S.typhii*, (Thaver D. et al., 2009). CAP is being used in developing countries for patients of all age groups (Weber, H. W. et al., 1999)

Floroquinolones have come up as an safe and efficient first line antibiotic alternative but significant differences in clinical manifestations usually occur (Thaver D. et al., 2009).

Use of CAP is controversial especially in the light of such a long list of alternative antibiotics. For the patients, still sticking to CAP prescription, it is recommended to keep a routine check of Hgb, WBC, RBC, platelet and Reticulocyte count. Even a slight increase in plasma concentration should lead to immediate stoppage of drug continuation.

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