Drug Information Bulletin

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Content

Editorial

Recent steps of Competition Commission of India (CCI) were welcomed by the health care experts, as they felt that this steps will encourage improving access to medicines to the general mass in India.

In a recent order the Competition Commission of India (CCI) has imposed fine in the tune of about 18 crores on Bengal Chemists & Druggist Association (BCDA) and its office bearers & executive council members due to their anticompetitive activities. As per the order passed on 11th February 2014 "It has come clear during the investigation that BCDA and its District and Zonal committees are engaged in anticompetitive practices of directly or indirectly determining the sale prices of drugs and controlling or limiting the supply of drugs through concerted and restricted practices in violation of Section 3(3) (a) and (b) read with Section 3(1) of the Act. " On the basis of their observation the Commission decided to impose a penalty on the BCDA & it's those office bearers who are directly responsible for running its affairs and play lead role in decision making @10% and on the executive committee members @7%, of their respective turnover/income/receipts based on the financial statements filed by them (http://www.cci.gov.in/May2011/OrderOfCommission/27/022012.pdf).

Earlier on the basis of a complaint by a distributor in Orissa, the CCI conducted an investigation and concluded that AIOCD and its associated bodies were infringing Sections 3(3) (A) and 3(3) (B) of the Act. The Commission has found these practices are anticompetitive and ordered the trade body to desist from such activities. Commission has also directed the AIOCD vide order dated 19.02.13 to file an undertaking that the practices carried on by it and its members regarding grant of NOC for appointment of stockiest, fixation of trade margins, collection of PIS (product information service) charges and boycott of products of pharmaceutical companies have been discontinued within 60 days from the date of receipt of this order. CCI also imposed a penalty of Rs.47, 40,613 to be paid by AIOCD.

Dr. Subhash C. Mandal
Editor

Pain Meds Fight Bacteria

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of compounds designed to reduce pain, fever, and inflammation. A few studies have suggested they may also possess antibacterial properties. In a paper published today (March 13) in *Chemistry & Biology*, researchers from the University of Wollongong in Australia have demonstrated that three NSAIDs exert weak antibacterial activity, and presented evidence that they do so by blocking the DNA polymerase sliding clamp, which is crucial for bacterial DNA replication.

"This is an interesting paper showing good evidence for biochemical inhibition of the DNA polymerase sliding clamp by a few NSAIDs," said Thomas Keating, a principal scientist at AstraZeneca Infection Innovative Medicines in Waltham, Massachusetts, in an e-mail to *The Scientist*. The causal link to the observed antibacterial effects is tenuous, he added, but the sliding clamp is "an interesting, novel antibacterial target."

"The fact the molecules tested are NSAIDs is not of great importance, given that the activity is too weak to be useful," added Keating. "The compounds are best viewed as leads that are quite a ways off from clinical candidacy."

Richard Ebright, a molecular biologist at Rutgers University in New Jersey, is more critical. "I cannot be supportive about the prospect that these results will inform the design of new antibacterial therapeutics," he said. "There is no compelling evidence that the replication-inhibitory activity is responsible for the antibacterial activity."

Aaron Oakley, a biological chemist at the University of Wollongong and senior author of the paper, recognizes that "the story is incomplete." But, he added, "our best explanation at this stage is that these compounds are binding to the DNA clamp."

The DNA polymerase sliding clamp is a donut-shaped structure forming part of an enzyme that synthesizes DNA molecules from nucleotide building blocks. It serves as a critical hub for protein-protein interactions during DNA replication and repair, and is conserved across bacterial species, which makes it a promising target for novel antibacterial agents, said Oakley.

When his team screened for compounds that inhibit the sliding clamp, they found one with a chemical structure similar to that of carpofren, an NSAID used in veterinary medicine. This led them to see if other anti-inflammatory drugs might have similar effects on the sliding clamp, and to explore whether such effects could be linked to antibacterial activity.

Of the 20 anti-inflammatory drugs the team tested, five showed binding affinity with the sliding clamp of in vitro *Escherichia coli*. Three NSAIDs in particular—carprofen, bromfenac, and vedaprofen—showed the strongest effects. X-ray crystallography revealed that these drugs bind to the same site that many proteins need to bind to for DNA replication. The same three compounds inhibited DNA replication in *E. coli*, while less potent sliding-clamp binders showed much weaker effects or no inhibition.

The researchers also tested the drugs for antibacterial activity on four species—*E. coli, Acinetobacter baylyi, Staphylococcus aureus*, and *Bacillus subtilis.* Potency varied across species, but in general the drugs that best blocked the sliding clamp had the highest levels of bactericidal activity. NSAIDs that did not inhibit the

sliding clamp, on the other hand, showed negligible or very low antibacterial activity, suggesting that there might be a connection between sliding clamp inhibition and antibacterial effect.

Oakley and his colleagues said their results show that some NSAIDs inhibit DNA replication in *E.coli* in vitro by binding to the sliding clamp and thereby preventing other proteins from binding. However, the authors stop short of claiming that the antibacterial activity is a result of sliding clamp inhibition.

"That's the correct interpretation in my view," said Keating. The authors still need to establish the causal link, he added, "but given the strong structural biology in this paper and the established in vitro assays, the tools are certainly present to conduct a rational, structure-based drug design program."

Ebright is not convinced. "The compounds analyzed have low sliding-clamp binding affinities in vitro, low replication-inhibitory activities in vitro, and low antibacterial activities in culture," he said. The minimum concentrations required to exert these effects are "approximately an order of magnitude higher than those of typical advanceable antibacterial lead compounds," he added.

Oakley acknowledged that the compounds are weak binders of the sliding clamp, but added that his team's validation of a potential antibacterial target was the crux of this work. "The point is that they work at all, which shows that we can target the sliding clamp in living bacteria," he said. "It's early days, of course, but we desperately need new antibiotics with novel modes of action so the demonstration that the sliding clamp is a valid target could be important." He also noted that they have developed more potent inhibitors of the DNA-clamp that have superior antibacterial activity.

In that respect, Keating cautiously agreed. "This work provides some new lead compounds," he said. "How promising they are will depend on how quickly the potency can be improved, whether the linkage to microbiological activity can be shown, and what the unknown liabilities of the target might be.

"In antibacterial discovery, all of the hard questions and answers come later," said Keating.

Z. Yin et al., "DNA replication is the target for the antibacterial effects of nonsteroidal anti-inflammatory drugs," *Chemistry & Biology*, 21:1-7, 2014.

Source: http://www.the-scientist.com/?articles.view/articleNo/39424/title/Pain-Meds-Fight-Bacteria/

UK to launch early access to drugs plan

Part of the Department of Health's Early Access Scheme – and following Prime Minister David Cameron's pledge in 2011 to improve early access – the policy, still to be approved, would look to cut the time from bench to bedside to about five years.

News of the launch of the scheme was reported by The Telegraph, which had seen official documents outlining that the scheme would apply to "innovative drugs for serious illnesses for which there is no existing treatment or where the current medicines are inadequate". Promising new drugs would also be designated with a "breakthrough" status, the newspaper adds.

Early access would be dependent on safety data, and patient and doctor consent, according to the documents.

Source: Pharmatimes Online

Only 89 out of 3458 deaths could be attributed to clinical trials during 2005-13: Health ministry

Even as the Swasthya Adhikar Manch, fighting a case on clinical trials in the Supreme Court, claimed that as many as 3458 people died during the trials in the last nine years including 590 in the year of 2013 alone, the government contented that only 89 deaths could be attributed to clinical trials.

Based on the details given by the government earlier, the NGO pointed out that from January 2005 to December 2012, as many as 2644 people died during the trials, while another 224 died between July 2012 to December 2012. The total number of serious adverse effects since from January 2005 to December 2013 stood at 14320, including 1122 cases during 2013, according to the affidavit by the NGO during the case hearing recently in the Supreme Court.

However, the government claimed that only 506 SAEs and 89 deaths were related to trials while the rest were unrelated. The government also said the compensations were paid in all 89 cases.

Following this huge difference in number, the SC has now asked the Ministry of Health and Family Welfare to provide data related to deaths and SAEs in four weeks, and do detailed review of new chemical entities and global clinical trials as per its earlier order of October 21, 2013.

“Look, it is not a question of one, two or three deaths. The figures say that there were 3,458 deaths. It is a very serious matter and disturbing. We want to know what is the mechanism that you have put in place to prevent it,” says the bench of Justices R M Lodha and Kurien Joseph.

Swasthya Adhikar Manch filed the case in February, 2012, seeking to streamline the clinical trial sector and against the malpractices in the sector by the companies.

Sanjay Parikh, appearing for the petitioner, mentioned that in the affidavits filed in December 2012 and on 29 January 2014 along with information provided on 14th February 2014, neither the Technical Committee nor the Apex Committee has given the details of their evaluation as per the three parameters given in the order dated 21-10-2013, instead they have merely rubber stamped their decisions.

The petitioner said the Ministry was not forthcoming about details regarding the approvals, particularly whether the approvals were granted by the Technical Committee and the Apex Committee only after considering the three parameters which were directed to be followed, i.e. (i) safety and efficacy, particularly in terms of risk and benefit to patient; (ii) innovation vis-à-vis existent therapeutic option; (iii) unmet need in the country.

The counsel also pointed that the ministry has not disclosed important details regarding new chemical entities such as for what health purpose were they required to be tested through clinical trials, whether these NCEs were subjected to clinical trials outside India, when did these companies apply for trial, when were they approved by the NDACs and when did the DCGI grant permission.

The health ministry had already confirmed that the 215 Bhopal gas victims who were subjects of clinical trials were not paid the requisite compensation and that the SAEs including death cases were not reported on time, the NGO said.

Source: Pharmabiz.com