Corticosteroids and erythropoeitin-receptor agonists

The excellent meta-analysis by Ryan Zarychanski and associates demonstrated that the use of erythropoietin-receptor agonists in critically ill patients does not improve clinically important outcomes.[1] Interestingly, the potential drug interaction with corticosteroids was not considered in the study.[1] Corticosteroids are now widely administered in critical care settings for adrenal supplementation and attenuation of the inflammatory and immune response.[2] It is probable that the lack of therapeutic effect for erythropoietin-receptor agonists in the trials conducted thus far could be explained by the fact that a substantial number of the participants would also have been receiving corticosteroids that interfered with or blunted the efficacy of the erythropoietin-receptor agonists.

There is experimental and molecular evidence of the negative effects of corticosteroids on the efficacy of erythropoietin-receptor agonists. An experimental study of spinal cord injury showed that coadministration of the corticosteroid methylprednisolone sodium succinate antagonized the protective effects of erythropoietin-receptor agonists, even though the erythropoietin receptor was upregulated normally after injury.[3]

Cellular signalling pathways for the activation of the erythropoietin receptor may further explain why corticosteroids blunt the actions of erythropoietin-receptor agonists. JUN N-terminal kinase and p38 (members of the mitogen-activated protein kinase family of serine-threonine kinases) are important in erythropoietin signalling.[4] These pathways are activated as a result of cellular stress but may also play a role in the proliferation, survival or differentiation of many cell types induced by growth factors. Corticosteroids have been shown to induce the rapid and sustained expression of dual-specificity phosphatase 1 (also known as mitogen-activated protein kinase phosphatase 1), which is a particularly effective inhibitor of the JUN N-terminal kinase and p38 mitogen-activated protein kinase signalling pathways.[5] Thus, the beneficial effects of erythropoietin-receptor agonists are mediated by the JUN N-terminal kinase and p38 cellular signalling pathways, whereas the anticytokine effects of corticosteroids are mediated by inhibition of these 2 pathways.

A detailed subgroup reanalysis of the patients in the meta-analysis who were receiving both corticosteroids and erythropoietin-receptor agonists is warranted. It is likely that between 25% and 30% of the participants received a corticosteroid. Experimental data suggest that corticosteroids and erythropoietin-receptor agonists should not be coadministered to patients because the therapeutic effects of the erythropoietin-receptor agonists are likely to be blunted.

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Competing interests: None declared.

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DOI:10.1503/cmaj.1070144

Corrections

The News article "New dosage limits for medical marijuana: But where's the science?"[1] contained an error in a cited study (*IDrugs* 2004;7:464-70). The study authors recommend a dose range of 0.05–7.40 g per day, *depending* on the level of tetrahydrocannabinol in the marijuana, which varied from 5%–30%. *CMAJ* apologizes for any inconvenience this error may have caused.

REFERENCE

1. Comeau P. New dosage limits for medical marijuana: But where's the science? *CMAJ* 2007;177:556-7.

DOI:10.1503/cmaj.071651

The Salon article "Reconsidering survival"[1] contained an error in the author information. Mark Leith is *teaching* psychotherapy at the University of Toronto. *CMAJ* apologizes for any inconvenience this error may have caused.

REFERENCE

1. Leith M. Reconsidering survival. *CMAJ* 2007;177:1148.

DOI:10.1503/cmaj.071652

The News article "New editor to increase systematic reviews and transfer knowledge"[1] contained an error. Dr. Sharon Straus is *CMAJ*'s new Section Editor, Reviews *and* continues to hold the position of director of the Knowledge Transfer Program for the Calgary Health Region. The *CMAJ* apologizes for any inconvenience this error may have caused.

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1. Eggertson E. New editor to increase systematic reviews and transfer knowledge. *CMAJ* 2007;177:706-7.

DOI:10.1503/cmaj.071650

The News article "Health authority bans pharmacy shadowing"[1] contained an error. The people who crafted the ban should have been identified as representatives from the Departments of Medicine Administration, Pharmacy Administration and Nursing Administration, in consultation with a medical ethicist. *CMAJ* apologizes for any inconvenience this error may have caused.

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1. Jones D. Health authority bans pharmacy shadowing. *CMAJ* 2007:177;1339-40.

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