噴霧吸入劑混合液相容性與噴霧過程中混合液滲透壓變化之評估研究

Compatibility of Nebulizer Solution Admixtures and Osmolality Changes during Nebulization

中文摘要

本研究探討 N-acetylcysteine (NAC)的氧化降解速率與噴霧吸入劑混合液：NAC nebulizer solution 與 fenoterol inhalant solution 混合液、NAC nebulizer solution 與 ipratropium nebulizer solution 混合液，以及 ipratropium nebulizer solution 與 fenoterol inhalant solution 混合液於室溫下的相容性。除藥品安定性外，對於和噴霧吸入安全性有關的因子如溶液滲透壓也進行評估研究。N,N’-diacetylcystine (DiNAC)爲 NAC 氧化降解的主要產物。NAC 溶液於封閉系統中，7 小時內氧化降解比率小於 10%，並依循僞零級反應進行氧化降解。利用 NAC 僞零級氧化降解速率常數計算 NAC 於對照組溶液，NAC nebulizer solution 與 ipratropium nebulizer solution 混合液，以及 NAC nebulizer solution 與 fenoterol inhalant solution 混合液中，降解至 90%所需時間(t90%)分別爲 7.22、6.76 與 10.30 小時。Fenoterol inhalant solution 與 NAC nebulizer solution 混合後會因混合液 pH 值偏鹼性(pH » 8)而使得 fenoterol 發生氧化降解成爲較不具交感神經活性的醌類化物，同時也造成 NAC 的氧化降解速率減緩。Ipratropium nebulizer solution 與 NAC nebulizer solution 混合後，ipratropium 濃度會因氫氧離子所催化的酯類水解而下降，一小時後 ipratropium 所餘濃度百分比爲 92.61 ± 2.24%。Ipratropium nebulizer solution 與 fenoterol inhalant solution 混合液於 7 小時內兩藥品所餘濃度百分比皆大於 92%。NAC nebulizer solution 爲高張溶液，因此，當單獨噴霧給予，和 fenoterol inhalant solution 或是 ipratropium nebulizer solution 混合後合併給予，應在進行噴霧前先以 0.45% NaCl (1/2 NS)稀釋，以降低溶液的滲透壓。儲液槽內藥品溶液滲透壓會隨噴霧時間因濃縮作用而上升，因此需注意在接近噴霧結束時，因滲透壓變化所可能引起的咳嗽或支氣管收縮等不良反應。

英文摘要

Kinetics of N-acetylcysteine (NAC) oxidation and the compatibility of NAC-fenoterol nebulizer solution, NAC-ipratropium nebulizer solution or an admixture containing ipratropium and fenoterol were studied at room temperature. Osmolality changes during nebulization were also measured. The result that molar concentration of NAC plus twice that of N,N’-diacetylcystine (DiNAC) at each sampling time was equal to the initial sum was indicative of DiNAC being the main degradation product during NAC oxidation. The loss of NAC by auto-oxidation in solution in a closed system

divided into a gaseous (air) and an aqueous phase followed pseudo-zero-order reaction during the study period (7 hours), in which the fractional decomposition of NAC was less than 10%. The 90% fractional life of NAC was prolonged when admixed with fenoterol to 10.30 hours as compared to 7.22 and 6.76 hours in NAC control solution and when admixed with ipratropium, respectively. Alkaline admixture of NAC and fenoterol contributed to increased fenoterol oxidation to less sympathomimetically potent quinones and decreased NAC oxidation rate. Admixing ipratropium with NAC raised the solution pH from acid to alkaline, and ipratropium was subject to hydroxyl ion catalyzed hydrolysis. The percentage remaining of ipratropium after one-hour admixing with NAC was 92.61 ± 2.24%. The admixture containing ipratropium and fenoterol was stable up to 7 hours, as indicated by less than 10% loss of each drug. Simultaneous administration of a hyper-osmolal solution of NAC with fenoterol or ipratropium was advised to be diluted with 0.45% NaCl (1/2 NS) to decrease the initial osmolality. Osmolality increased with nebulization time and medical staffs should watch for possible bronchoconstriction or coughing near the end of nebulization.